10/ 023,099

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 01   INPADOC: New family current-awareness alert (SDI) available
 NEWS  4  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
 NEWS  5  SEP 01   New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
 NEWS  6  SEP 27   STANDARDS will no longer be available on STN
 NEWS  7  SEP 27   SWETSCAN will no longer be available on STN
 NEWS  8  OCT 28   KOREAPAT now available on STN
 NEWS  9  NOV 18   Current-awareness alerts, saved answer sets, and current
                   search transcripts to be affected by CERAB, COMPUAB, ELCOM,
                   and SOLIDSTATE reloads
 NEWS  10 NOV 30   PHAR reloaded with additional data

 NEWS EXPRESS  OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:07:18 ON 30 NOV 2004

=> file reg
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:07:50 ON 30 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
```

10/ 023,099

provided by InfoChem.

STRUCTURE FILE UPDATES: 28 NOV 2004 HIGHEST RN 790189-55-8
DICTIONARY FILE UPDATES: 28 NOV 2004 HIGHEST RN 790189-55-8

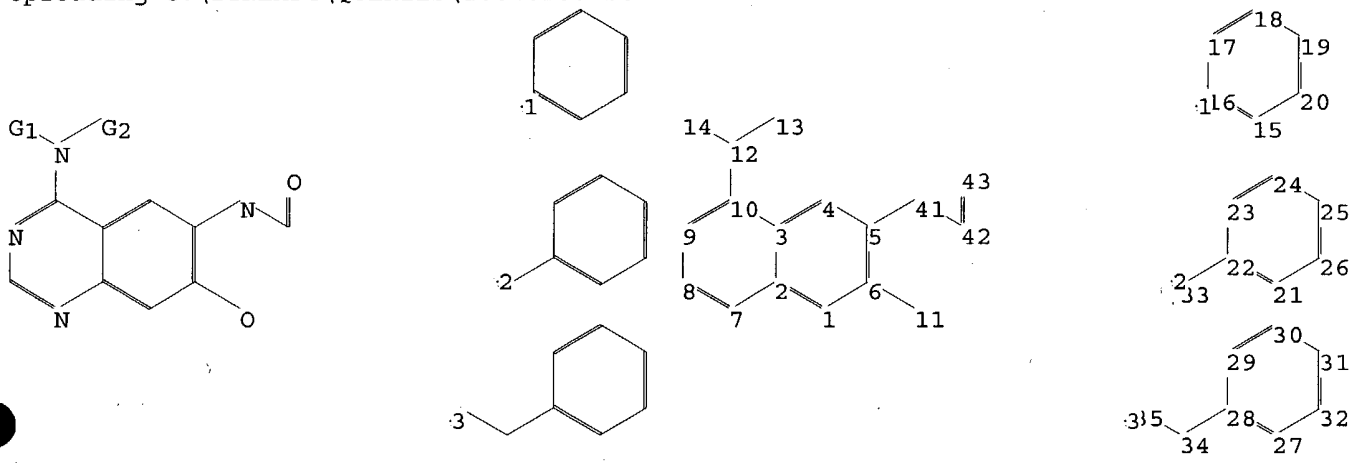
TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\STNEXP4\QUERIES\10016280.str



chain nodes :
11 12 13 14 33 34 35 41 42 43
ring nodes :
1 2 3 4 5 6 7 8 9 10 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
chain bonds :
5-41 6-11 10-12 12-13 12-14 22-33 28-34 34-35 41-42 42-43
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18 18-19 19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31 31-32
exact/norm bonds :
5-41 6-11 10-12 12-13 12-14 41-42 42-43
exact bonds :
22-33 28-34 34-35
normalized bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18 18-19 19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31 31-32
isolated ring systems :
containing 1 : 15 : 21 : 27 :

G1:H,Ak

10/ 023,099

G2:[*1],[*2],[*3]

Hydrogen count :
8:= exact 1
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom
21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom
31:Atom 32:Atom 33:CLASS 34:CLASS 35:CLASS 41:CLASS 42:CLASS 43:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful
FULL SEARCH INITIATED 14:08:15 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 437 TO ITERATE

100.0% PROCESSED 437 ITERATIONS 422 ANSWERS
SEARCH TIME: 00.00.03

L2 422 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.42	155.63

FILE 'CAPLUS' ENTERED AT 14:08:26 ON 30 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 30 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 29 Nov 2004 (20041129/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l2
L3 73 L2

=> d l3 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 73 ANSWERS - CONTINUE? Y/(N):y

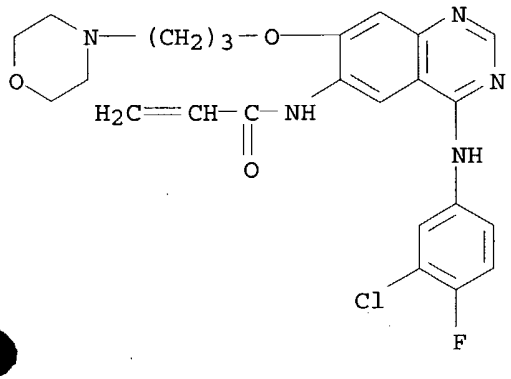
L3 ANSWER 1 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:965067 CAPLUS
TITLE: Combinations for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis
INVENTOR(S): Hilberg, Frank; Solca, Flavio; Stefanic, Martin Friedrich; Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004096224	A2	20041111	WO 2004-EP4363	20040424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1473043	A1	20041103	EP 2003-9587	20030429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.:
EP 2003-9587 A 20030429
EP 2004-508 A 20040113
EP 2004-1171 A 20040121

AB The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination prepns. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further chemotherapeutic or naturally occurring semisynthetic or synthetic agents.

IT INDEXING IN PROGRESS
IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug combinations for diseases involving cell proliferation and migration or apoptosis or angiogenesis including protein tyrosine kinase receptor antagonists and radiotherapy)
RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 2 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:902075 CAPLUS
DOCUMENT NUMBER: 141:361105
TITLE: Methods for detection of ErbB cell surface receptor complexes as cancer biomarkers and therapeutic effectiveness of cleavage thereof
INVENTOR(S): Chan-Hui, Po-Ying; Salimi-Moosavi, Hossein; Shi, Yining; Singh, Sharat; Dua, Rajiv; Mukherjee, Ali; Pidaparthi, Sailaja
PATENT ASSIGNEE(S): Aclara Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 29
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004091384	A2	20041028	WO 2004-US9715	20040330
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004126818	A1	20040701	US 2003-623057	20030717

PRIORITY APPLN. INFO.:		
US 2003-459888P	P	20030401
US 2003-623057	A	20030717
US 2003-494482P	P	20030811
US 2003-508034P	P	20031001
US 2003-512941P	P	20031020
US 2003-523258P	P	20031118
US 2002-398724P	P	20020725

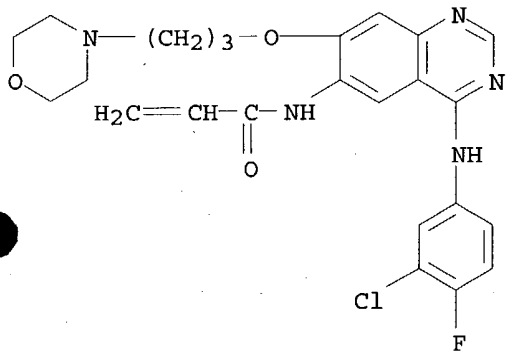
AB The invention is directed to a new class of biomarker in patient samples comprising dimers of ErbB cell surface membrane receptors. In one aspect,

the invention includes a method of determining the status of a disease or healthful condition by correlating such condition to amts. of one or more dimers of ErbB cell surface membrane receptors measured directly in a patient sample, in particular a fixed tissue sample. In another aspect, the invention includes a method of determining a status of a cancer in a specimen from an individual by correlating measurements of amts. of one or more dimers of ErbB cell surface membrane receptors in cells of the specimen to such status, including presence or absence of a pre-cancerous state, presence or absence of a cancerous state, prognosis of a cancer, or responsiveness to treatment. Preferably, methods of the invention are implemented by using sets of binding compds. having releasable mol. tags that are specific for multiple components of one or more types of receptor dimers. After binding, mol. tags are released and separated from the assay mixture for anal.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for detection of ErbB cell surface receptor complexes as cancer biomarkers and therapeutic effectiveness of cleavage thereof)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 3 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:719893 CAPLUS
DOCUMENT NUMBER: 141:243560
TITLE: Preparation of 4-anilinoquinazolines as tyrosine kinase inhibitors for the treatment of tumors
INVENTOR(S): Himmelsbach, Frank; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
SOURCE: Ger. Offen., 21 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10307165	A1	20040902	DE 2003-10307165	20030220
WO 2004074263	A1	20040902	WO 2004-EP1398	20040214

10/ 023,099

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI, NI, NO

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2003-10307165 A 20030220

OTHER SOURCE(S): MARPAT 141:243560

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = H, alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3 = H, halo, OH, etc.; R4, R5 = H, alkyl; X = C(CN), N with provisos; Z = (un)substituted heterocycle] and their pharmaceutically acceptable salts ands formulations were prepared For example, coupling of 4-[2,2-dimethoxyethyl]homomorpholine and phosphonate II, e.g., prepared from di-Et carboxymethylphosphonate and N4-(3-chloro-4-fluorophenyl)-7-[[(3S)-tetrahydro-3-furanyl]oxy]-4,6-quinazolinediamine, afforded claimed anilinoquinazoline III in 63% yield. In human epidermal growth factor receptor binding assays, anilinoquinazoline III exhibited an IC50 value of 1.5 nM. Compds. I are claimed useful for the treatment of tumors, i.e, prostate benign hyperplasia.

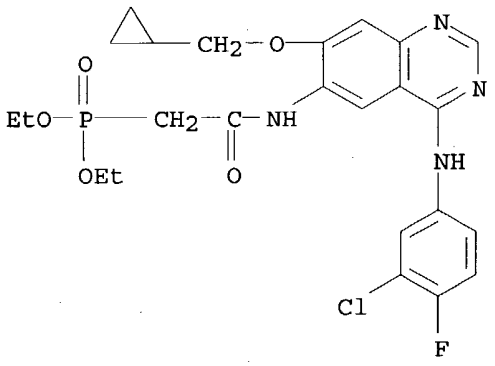
IT **365532-31-6P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 4-anilinoquinazolines as tyrosine kinase inhibitors for the treatment of tumors)

RN 365532-31-6 CAPLUS

CN Phosphonic acid, [2-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-2-oxoethyl]-, diethyl ester (9CI) (CA INDEX NAME)



L3 ANSWER 4 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:717320 CAPLUS

DOCUMENT NUMBER: 141:288467

TITLE: Canertinib (Pfizer)

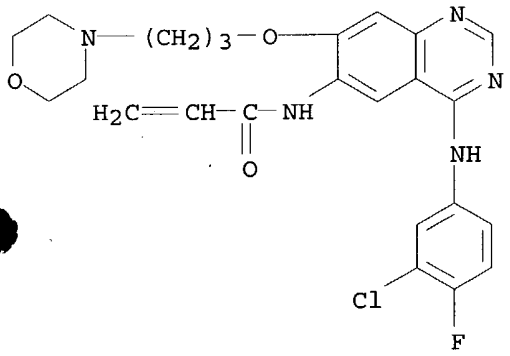
10/ 023,099

AUTHOR(S): Galmarini, Carlos Maria
CORPORATE SOURCE: INSERM 590. 8, University of Lyon, Lyon, 69373/08, Fr.
SOURCE: IDrugs (2004), 7(1), 58-63
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Canertinib, a water-soluble, orally available analog of PD-169414, is an epidermal growth factor tyrosine kinase inhibitor under development by Pfizer Inc as a potential treatment for cancer. This article describes the synthesis and structure-activity relations of the compound, its preclin. development, metabolism and pharmacokinetics, toxicity, clin. development, and side effects and contraindications.

IT **267243-28-7P**, Canertinib
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and pharmacol. of canertinib, an angiogenesis inhibitor (epidermal growth factor inhibitor), for the treatment of cancer)

RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



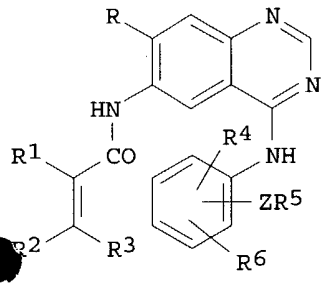
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:654786 CAPLUS
DOCUMENT NUMBER: 141:174186
TITLE: Preparation of substituted quinazolines for use in pharmaceutical compositions as inhibitors of tyrosine kinases
INVENTOR(S): Barth, Hubert; Bridges, Alexander James; Heemstra, Ronald J.; Horne, Nicole Marcia; Hughes, Robert Craig; Jacks, Thomas Elliott; McNamara, Dennis Joseph; Schneider, Simon; Steiner, Klaus; Toogood, Peter Laurence; Winters, Roy Thomas
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

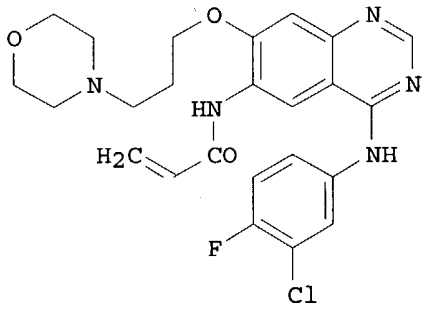
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2004158065	A1	20040812	US 2004-771774 20040204
WO 2004069791	A2	20040819	WO 2004-IB321 20040203
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI			
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
NL 1025414	A1	20040806	NL 2004-1025414 20040205
PRIORITY APPLN. INFO.:			US 2003-445095P P 20030205
OTHER SOURCE(S):	MARPAT 141:174186		

GI



I



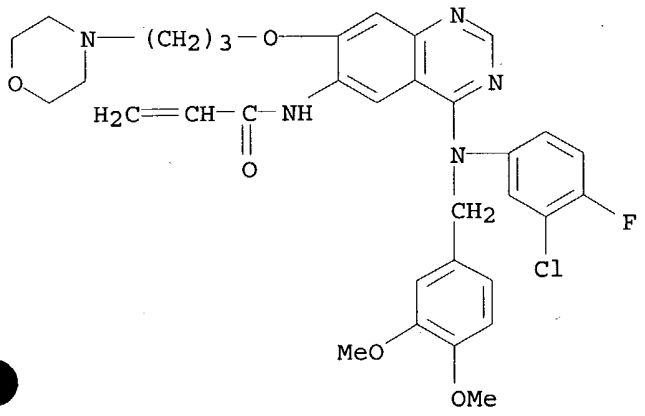
II

AB Quinazoline amines, such as I [R1, R2, R3 = H, NO2, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, carboxy, etc.; R4, R6 = H, OH, CN, NO2, CF3,halogen, alkyl, alkoxy, alkylamino, alkylthio, alkylsulfinyl, acyl, carbamoyl, etc.; R5 = aryl or heteroaryl, such as Ph, pyridyl, furyl, thiazolyl, etc.; ZR5 = H, halogen ; Z = linking group, such as alkylene, etc.; R = OH, SH, NH2, heterocyclylalkyloxy, etc.] were prepared for therapeutic use as inhibitors of tyrosine kinases and may be useful for treatment of cancer, restenosis, atherosclerosis, endometriosis and psoriasis. Thus, N-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl]-acrylamide(II) was prepared via a series of synthetic steps starting form acryloyl chloride, 3-(morpholin-4-yl)propan-1-ol, 3-chloro-4-fluoroaniline, and 4-chloro-7-fluoro-6-nitroquinazoline.

IT **736173-03-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of substituted quinazolines for use in pharmaceutical compns. as inhibitors of tyrosine kinases)

RN 736173-03-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)[(3,4-dimethoxyphenyl)methyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 6 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:633433 CAPLUS
DOCUMENT NUMBER: 141:167750
TITLE: Novel irreversible inhibitors of epidermal growth factor receptor tyrosine kinase and uses thereof for therapy and diagnosis
INVENTOR(S): Mishani, Eyal; Rozen, Yulia; Abourbeh, Galith; Levitzki, Alexander
PATENT ASSIGNEE(S): T.K. Signal Ltd., Israel
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

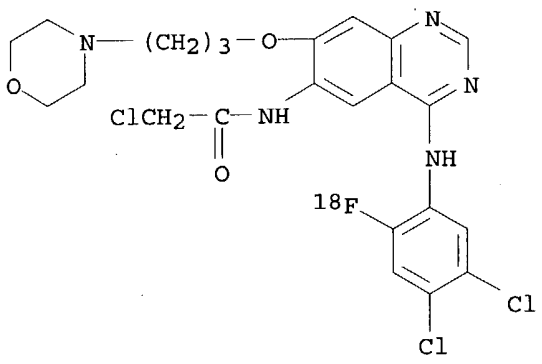
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004064718	A2	20040805	WO 2004-IL68	20040122

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

PRIORITY APPLN. INFO.: US 2003-441779P P 20030123
OTHER SOURCE(S): MARPAT 141:167750

AB Novel epidermal growth factor receptor tyrosine kinase (EGFR-TK) irreversible inhibitors, pharmaceutical compns. including same and their use in the treatment of EGFR-TK related diseases or disorders are disclosed. Novel radiolabeled EGFR-TK irreversible inhibitors as their use as biomarkers for medicinal radioimaging such as Positron Emission Tomog. (PET) and Single Photon Emission Computed Tomog. (SPECT) and as radiopharmaceuticals for radiotherapy are further disclosed.

IT **733009-47-7P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitors of EGFR tyrosine kinase for cancer therapy and diagnosis)
RN 733009-47-7 CAPLUS
CN Acetamide, 2-chloro-N-[4-[[4,5-dichloro-2-(fluoro-18F)phenyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



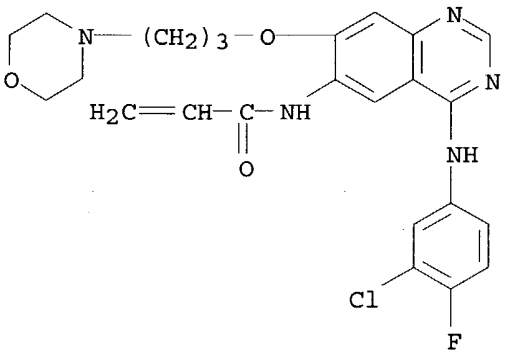
L3 ANSWER 7 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:533970 CAPLUS
DOCUMENT NUMBER: 141:65088
TITLE: Methods and compositions for the prevention or treatment of neoplasia comprising a COX-2 inhibitor in combination with an epidermal growth factor receptor antagonist
INVENTOR(S): Masferrer, Jaime
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 103 pp., Cont.-in-part of U.S. Ser. No. 470,951.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 21
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004127470	A1	20040701	US 2003-651916		20030829
PRIORITY APPLN. INFO.:			US 1998-113786P	P	19981223
			US 1999-470951	B2	19991222

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGF receptor antagonist. Compns., pharmaceutical compns. and kits are also described.

IT **267243-28-7**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR antagonist; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 8 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:533967 CAPLUS
DOCUMENT NUMBER: 141:65147
TITLE: Method for treating diseases associated with abnormal tyrosine kinase activity by administering a DNA methylation inhibitor and a tyrosine kinase inhibitor
INVENTOR(S): Lyons, John; Rubinfeld, Joseph
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. Ser. No. -71,849.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004127453	A1	20040701	US 2002-206854	20020726
US 2003147813	A1	20030807	US 2002-71849	20020207
WO 2003065995	A2	20030814	WO 2003-US3537	20030206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-71849 A2 20020207
US 2002-206854 A1 20020726

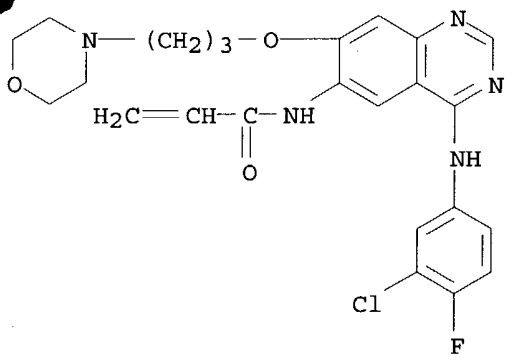
AB Methods are provided for treating diseases associated with abnormal activity of kinases. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amount; and administering a kinase inhibitor to the patient in therapeutically effective amount, such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat cancer associated with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (PI3K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor

family (FGFR) insulin receptor family, ephrin receptor family, Met family, Ror family, c-kit family, Src family, Fes family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Abl family.

IT **289499-45-2**, CI1033
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as EGFR tyrosine kinase inhibitor; treating diseases associated with abnormal tyrosine kinase activity by administering DNA methylation inhibitors and tyrosine kinase inhibitors)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 9 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:430979 CAPLUS
DOCUMENT NUMBER: 141:5495
TITLE: Altered patterns of protein phosphorylation associated with glioblastoma progression and their diagnostic detection with phospho-specific antibodies
INVENTOR(S): Mischel, Paul S.; Sawyers, Charles L.; Smith, Bradley L.; Crosby, Katherine
PATENT ASSIGNEE(S): The Regents of the University of California, USA; Cell Signaling Technology, Inc.
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004044218	A2	20040527	WO 2003-US35115	20031105

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,

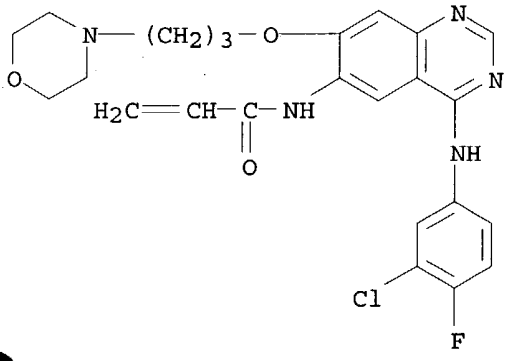
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004106141 A1 20040603 US 2003-701490 20031105
PRIORITY APPLN. INFO.: US 2002-423777P P 20021105

AB Proteins showing altered patterns of phosphorylation are identified for use in the diagnosis of gliomas, including glioblastoma multiforme. The proteins showing altered patterns of phosphoryaltion may also be targets for chemotherapy.

IT **289499-45-2**, CI 1033
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in treatment of glioma, selection of; altered patterns of protein phosphorylation associated with glioblastoma progression and their diagnostic detection with phospho-specific antibodies)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

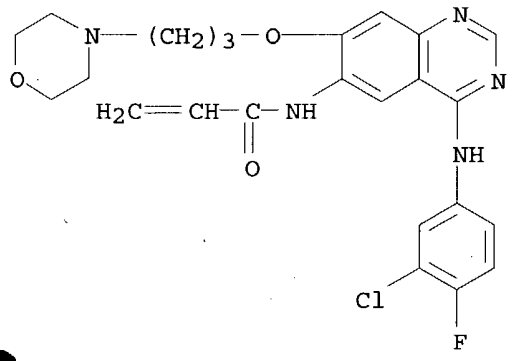
L3 ANSWER 10 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:424391 CAPLUS
DOCUMENT NUMBER: 141:49704
TITLE: Induction of apoptosis by ionizing radiation and CI-1033 in HuCCT-1 cells
AUTHOR(S): Murakami, Masateru; Sasaki, Tamito; Yamasaki, Souichirou; Kuwahara, Kenichi; Miyata, Hideki; Chayama, Kazuaki
CORPORATE SOURCE: Graduate School of Biochemical Sciences, Programs for Biochemical Research, Division of Frontier Medical Science, Department of Medicine and Molecular Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan
SOURCE: Biochemical and Biophysical Research Communications (2004), 319(1), 114-119
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CI-1033 is a quinazoline-based HER family tyrosine kinase inhibitor that is currently being evaluated as a potential anticancer agent. The present study examines the mol. mechanism by which CI-1033 induces apoptosis either as a single agent or in combination with radiation. Although

CI-1033 alone did not induce apoptosis, the simultaneous exposure of cells to CI-1033 and radiation induced significant levels of apoptosis. The sequential treatment of cells with CI-1033 followed by radiation induced an even greater effect with 62.6% of cells undergoing apoptosis but this enhanced effect was not seen if cells were treated first with radiation and then CI-1033. The combination treatment induces apoptosis of HuCCT-1 via upregulation of FasL and Bid cleavage. These data suggest that modulation of the Fas-FasL pathway and activation of Bid could be useful for increasing the anti-tumor effect of CI-1033 in this type of cancer.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(apoptosis induction by TK inhibitor CI-1033 alone or in combination with ionizing irradiation: FasL and Bid cleavage upregulation)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392613 CAPLUS
DOCUMENT NUMBER: 140:388248
TITLE: Nucleotide-binding protein-directed probes and their use in determining enzyme profiles
INVENTOR(S): Campbell, David Alan; Szardenings, Anna Katrin; Shreder, Kevin Robert; Betancort, Juan Manuel; Winn, David
PATENT ASSIGNEE(S): Activx Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004040003	A2	20040513	WO 2003-US34550	20031029
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,				

GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-422304P P 20021029

AB The present invention provides nucleotide binding protein-directed affinity probes (NBAPs), such as derivs. of 4-phenylaminoquinazoline, staurosporine, bis-indolemaleimide, pyrido[2,3-d]pyrimidine, and adenine, and methods for their use. The NBAP generally comprises the aforementioned targeting moiety, a reactive group (thiocyanate, maleimide, etc.), and a label (fluorescein, rhodamine, etc.). The subject methods and compns. can provide enhanced simplicity and accuracy in identifying changes in the presence, amount, or activity of nucleotide binding proteins in a complex protein mixture, preferably kinases, and most preferably active forms of kinases, using NBAPs that bind to target nucleotide binding protein(s).

IT **688024-56-8P**

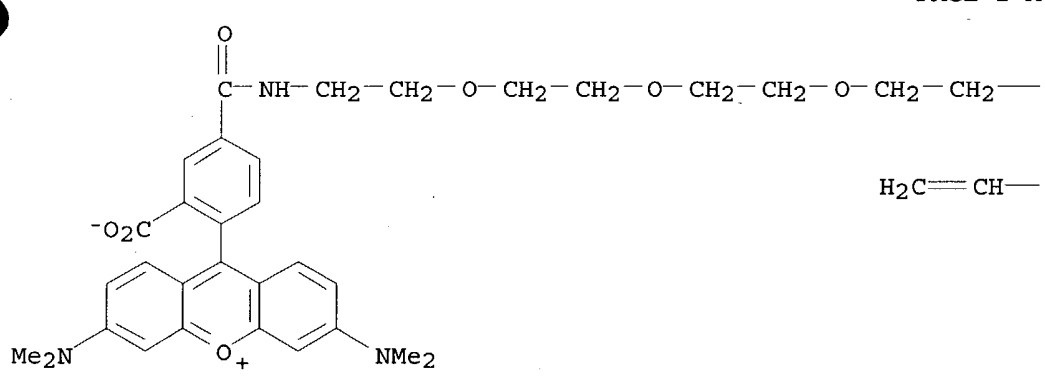
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)

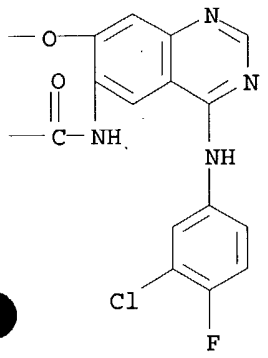
(nucleotide-binding protein-directed probes and their use in determining enzyme profiles)

RN 688024-56-8 CAPLUS

CN Xanthylium, 9-[2-carboxy-4-[13-[[4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]-1-oxo-5,8,11-trioxa-2-azatridec-1-yl]phenyl]-3,6-bis(dimethylamino)-, inner salt (9CI) (CA INDEX NAME)

PAGE 1-A





L3 ANSWER 12 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:354796 CAPLUS
DOCUMENT NUMBER: 140:368653
TITLE: Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
INVENTOR(S): Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035057	A1	20040429	WO 2003-GB4347	20031007

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-23854 A 20021012

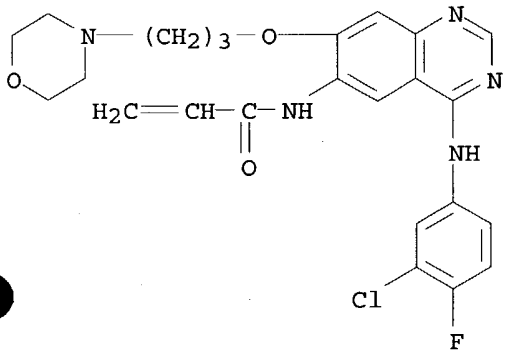
AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

IT **267243-28-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for treatment of cancer)

RN 267243-28-7 CAPLUS

10/ 023,099

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:280687 CAPLUS
DOCUMENT NUMBER: 140:296746
TITLE: Epidermal growth factor receptor inhibitors: a new prospective in the treatment of lung cancer
AUTHOR(S): Tiseo, M.; Loprevite, M.; Ardizzoni, A.
CORPORATE SOURCE: Division of Medical Oncology A Istituto Nazionale per la Ricerca sul Cancro Genova, Genoa, 16132, Italy
SOURCE: Current Medicinal Chemistry: Anti-Cancer Agents (2004), 4(2), 139-148
CODEN: CMCACI; ISSN: 1568-0118
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

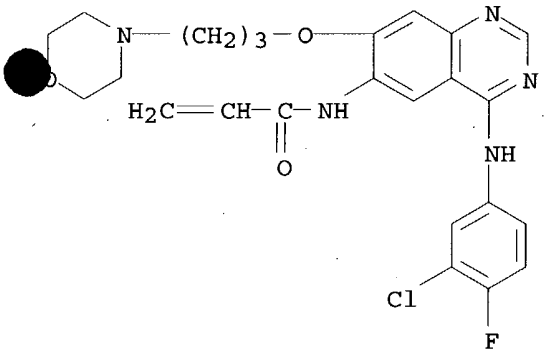
AB A review. Lung cancer is the leading cause of death worldwide. Current treatment modalities, including chemotherapy, radiotherapy and surgery, provide only limited improvement in the natural course of this disease. Therefore, the development of new therapeutic strategies is highly awaited. This review focuses on recent achievements on a novel class of anticancer drugs targeting the EGFR (Epidermal Growth Factor Receptor). The EGFR family is a group of four structurally similar growth factor receptors with tyrosine-kinase activity (EGFR, HER2/neu, ErbB-3, ErbB-4), which dimerize upon binding with a number of ligands, including EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor), allowing downstream transduction of mitogenic signals. Overexpression of EGFR and HER2 is frequently found in non-small-cell lung cancer (NSCLC), which accounts for over 80% of all malignant lung tumors, and has been associated with a worse clin. outcome. New agents developed to inhibit EGFR function include monoclonal antibodies and small-mol. receptor tyrosine-kinase inhibitors. In this review, results of most recent clin. with EGFR inhibitors including monoclonal antibodies, such as Trastuzumab (Herceptin), IMC-C225 (Cetuximab) and others (ABX-EGF, EMD 72000), and tyrosine-kinase inhibitors, such as ZD1839 (Gefitinib, Iressa), OSI-774 (Erlotinib, Tarceva) and others (CI-1033, GW2016), are summarized. In particular, final results of phase II (IDEAL 1 and 2) and III (INTACT 1 and 2) studies of ZD1839 are reported. In IDEAL trials (ZD1839 single agent in patients pre-treated with chemotherapy) there was clear evidence of tumor regression, symptoms improvement and overall clin. benefit, whereas in the two INTACT trials (ZD1839 in combination with standard platinum-based chemotherapy in chemo-naive patients) ZD1839 did not improve either survival or other clin. endpoints. Possible explanations

for these contradictory results and future perspectives are discussed.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor inhibitors in treatment of lung cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

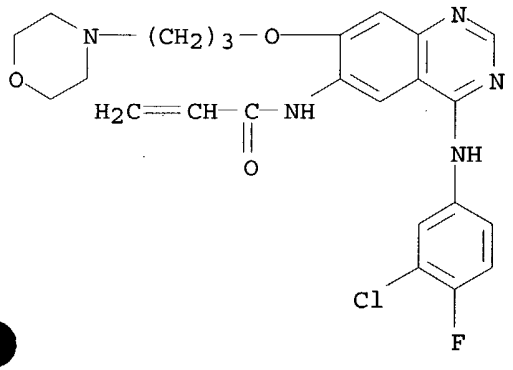
ACCESSION NUMBER: 2004:197494 CAPLUS
DOCUMENT NUMBER: 141:235330
TITLE: Emerging roles of targeted small molecule protein-tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Smith, John K.; Mamoon, Naila M.; Duhe, Roy J.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, 39216-4505, USA
SOURCE: Oncology Research (2003), 14(4/5), 175-225
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Targeted protein-tyrosine kinase inhibitors (PTKIs) comprise a new, rapidly evolving class of low mol. weight anticancer drugs. Two members of this class, imatinib (Gleevec) and gefitinib (Iressa), are currently approved for market use in the United States. This review discusses the scientific history behind these two PTKI drugs, including the role of the targeted kinase in cancer etiol., the biochem. of selective inhibition, the evaluation of clin. efficacy, and the mechanisms whereby drug resistance has emerged. Other PTKIs undergoing clin. evaluation are also described, including epidermal growth factor receptor kinase inhibitors (erlotinib, PKI166, and CI-1033) and PTKIs designed to disrupt tumor vascularization (SU5416, SU6668, SU11248, PTK787, and ZD6474). How might one apply current knowledge to the efficient development of new agents that would target as-yet-unexploited oncogenic PTKs such as chimeric anaplastic leukemia kinases or Janus kinases. Ideally, the targets should contain structurally distinct drug interaction epitopes, although it is

not necessary that these epitopes be unique to a single target, because effective drugs may inhibit multiple kinases involved in an oncogenic process. Oral availability is a highly desirable feature because daily oral administration can maintain a sustained efficacious plasma concentration, whereas intermittent parenteral administration may not. Perhaps most importantly, one must verify the presence of an appropriate mol. target on a case-by-case basis before selecting a patient for PTKI therapy. Thus, the development of molecularly targeted diagnostic tools will be crucial to the ultimate success of molecularly targeted PTKI therapy.

IT **289499-45-2**, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor kinase inhibitor CI-1033 is designed to disrupt tumor vascularization and used in treatment of cancer therapy)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 422 THERE ARE 422 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:182368 CAPLUS
DOCUMENT NUMBER: 140:229401
TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands
INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043388	A1	20040304	US 2002-234985	20020903

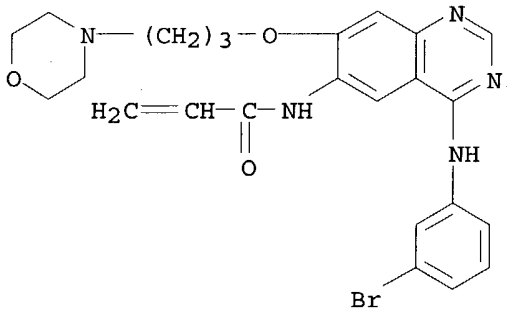
US 2003165873	A1	20030904	US 2002-91177	20020304
PRIORITY APPLN. INFO.:			US 2001-272932P	P 20010302
			US 2001-278233P	P 20010323
			US 2001-329437P	P 20011015
			US 2002-91177	A2 20020304

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Preparation of compds., e.g a methotrexate moiety linked by a polyethylene gycol moiety to dexamethasone, is described.

IT **198959-99-8D**, conjugates
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 198959-99-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 16 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:142967 CAPLUS
DOCUMENT NUMBER: 140:175126
TITLE: Therapeutic combinations of erb b kinase inhibitors and antineoplastic therapies
INVENTOR(S): Elliott, William Leon; Fry, David William
PATENT ASSIGNEE(S): Warner-Lambert Company Llc, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014386	A1	20040219	WO 2003-IB3388	20030728
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004067942	A1	20040408	US 2003-632281	20030801
PRIORITY APPLN. INFO.:			US 2002-401705P	P 20020807

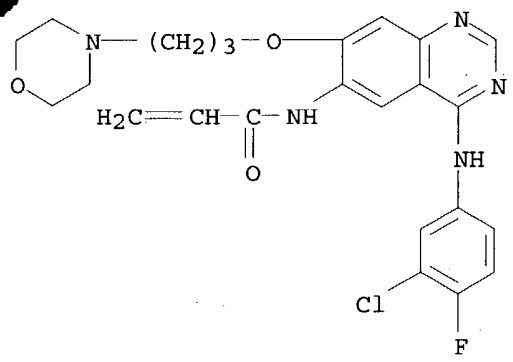
US 2003-462247P P 20030411

AB The invention describes administration of an irreversible tyrosine kinase inhibitor such as CI-1033 in combination with one or more other antineoplastic agent(s), or ionizing radiation is synergistic for treating cancer.

IT **267243-28-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:120750 CAPLUS
DOCUMENT NUMBER: 140:175121
TITLE: Therapeutic inhibition of protein kinases and a cellular ATP synthetic pathway in cancer cells
INVENTOR(S): Carson, Dennis A.; Rosenbach, Michael D.; Carrera, Carlos J.; Leoni, Lorenzo M.
PATENT ASSIGNEE(S): The Regents of the University of California, USA; Salmedix, Inc.
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004012769	A1	20040212	WO 2003-US24439	20030801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004096436	A1	20040520	US 2003-632592	20030801

10/ 023,099

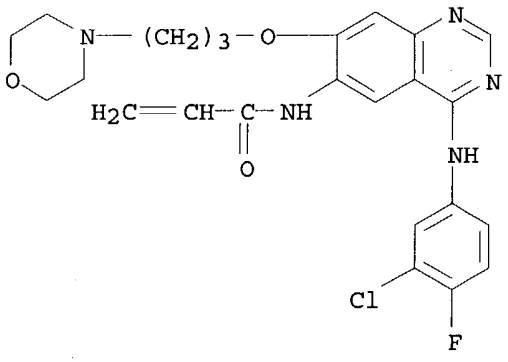
PRIORITY APPLN. INFO.: US 2002-400568P P 20020802

AB The present invention provides methods of treating cancer using inhibitors of protein kinases. The inhibitors of protein kinases are combined with agents that inhibit a cellular ATP synthetic pathway. Inhibitors of ATP synthesis include inhibitors of de novo purine biosynthesis, inhibitors of the salvage pathway of ATP biosynthesis, and inhibitors of the enzyme inosine monophosphate dehydrogenase.

IT **289499-45-2**, CI1033
RL: PAC (Pharmacological activity); BIOL (Biological study)
(receptor tyrosine kinase inhibitor; therapeutic inhibition of protein kinases and cellular ATP synthetic pathway in cancer cells)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 18 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:100947 CAPLUS
DOCUMENT NUMBER: 140:139486
TITLE: Method of treating cancer
INVENTOR(S): Potter, David A.
PATENT ASSIGNEE(S): Advanced Research & Technology Institute at Indiana University, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004010937	A2	20040205	WO 2003-US23437	20030728
WO 2004010937	A3	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004167139 A1 20040826 US 2003-629045 20030728

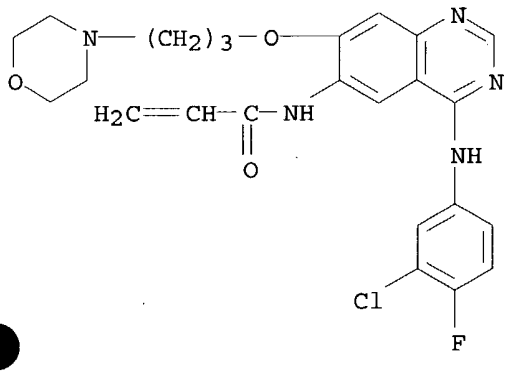
PRIORITY APPLN. INFO.: US 2002-399573P P 20020726

AB Methods for treating cancer are described here. The methods include administering to an HIV-neg. patient an m-calpain inhibitor such as ritonavir. Ritonavir or other m-calpain inhibitors can also be co-administered with other therapeutic agents such as a Cox-2 inhibitor, a taxane, or a proteasome inhibitor. Methods for determining whether a patient will respond to a particular method of treatment are also described herein.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treating cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 19 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:88605 CAPLUS

DOCUMENT NUMBER: 141:291342

TITLE: Radiosensitization by Pan ErbB Inhibitor CI-1033 in Vitro and in Vivo

AUTHOR(S): Nyati, Mukesh K.; Maheshwari, Divya; Hanasoge, Sheela; Sreekumar, Arun; Rynkiewicz, Susan D.; Chinnaiyan, Arul M.; Leopold, Wilbur R.; Ethier, Stephen P.; Lawrence, Theodore S.

CORPORATE SOURCE: Departments of Radiation Oncology, Ann Arbor Laboratories, Ann Arbor, MI, USA

SOURCE: Clinical Cancer Research (2004), 10(2), 691-700
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

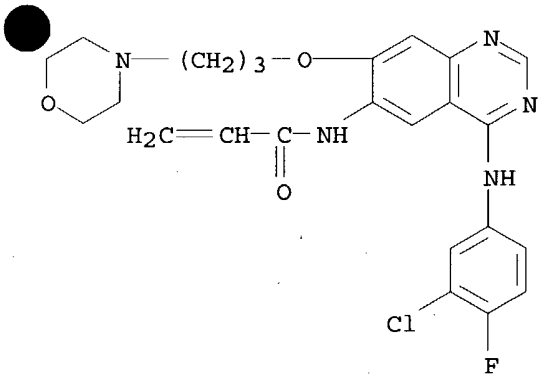
AB Overexpression of the ErbB family of receptor tyrosine kinases has been associated with uncontrolled growth of many tumor types and, therefore, presents a promising mol. target for cancer therapy. CI-1033 is a small mol. tyrosine kinase inhibitor that differs from other 4-anilinoquinazolines by being a pan ErbB (instead of epidermal growth factor receptor-specific) irreversible (instead of reversible) inhibitor.

Therefore, we investigated the antitumor effect of CI-1033 alone and in combination with ionizing radiation in vitro and in vivo. We selected three human colon carcinoma cell-lines (LoVo, Caco-2, which express activated epidermal growth factor receptor and ErbB-2 family members, and SW620, which does not), and analyzed the effects of CI-1033 both in vitro and in vivo. For in vivo studies LoVo and Caco-2 cells were implanted s.c. in the flank of nude mice. After the tumor reached .apprx.100 mm3, treatment was initiated with 20 mg/kg of CI-1033 (orally once daily x 5 for 3 successive weeks), radiation treatment (a total of 30 Gy given in 2 Gy once daily x 5 for 3 successive weeks), or a combination of both CI-1033 and radiation treatment. We found that exposure of LoVo and Caco-2, but not SW620 cells, to CI-1033 in the range of 1-3 μM could inhibit constitutive signaling by tyrosine kinases, arrest cell growth, inhibit cells in G1, stimulate expression of p53, and induce apoptosis. The inhibition of cell growth by CI-1033 seemed to produce only minimal radiosensitization in LoVo and Caco-2 cells. In contrast, the combination of CI-1033 and radiation produced significant ($P < 0.0005$ and $P = 0.0002$, resp.) and prolonged suppression of tumor growth in both the tumor types when compared with either treatment alone. These findings suggest that CI-1033 can increase the effectiveness of radiation therapy. The extent of suppression of tyrosine kinase activity by CI-1033, rather than the amount of activity in untreated cells, seemed to be more closely associated with the efficacy of combination treatment.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization by pan ErbB inhibitor CI-1033 in vitro and in vivo)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:88574 CAPLUS
DOCUMENT NUMBER: 141:309684
TITLE: Searching for reliable epidermal growth factor receptor response predictors: Commentary re M. K. Nyati et al., Radiosensitization by Pan-ErbB inhibitor CI-1033 in vitro and in vivo. Clin. Cancer Res., 10: 691-700, 2004

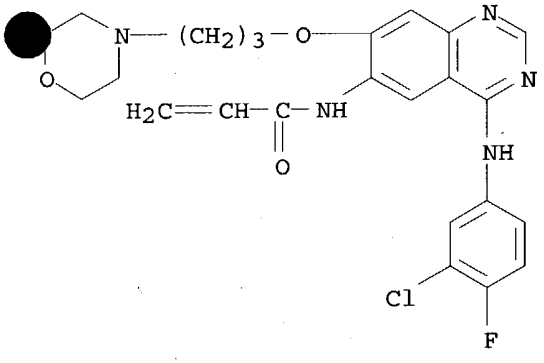
10/ 023,099

AUTHOR(S): Harari, Paul M.; Huang, Shyh-Min
CORPORATE SOURCE: Department of Human Oncology, University of Wisconsin School of Medicine and Comprehensive Cancer Center, Madison, WI, 53792, USA
SOURCE: Clinical Cancer Research (2004), 10(2), 428-432
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A polemic in response to Nyati et al. Clin. Cancer. Res: 691-700, 2004. The research of Nyati et al. (2004) entitled "Radiosensitization by pan ErbB inhibitor CI-1033 in vitro and in vivo" is reviewed with commentary and refs. Nyati et al. examined the impact of an irreversible pan ErbB tyrosine kinase inhibitor (CI-1033) across a series of colon cancer cell lines in vitro and in vivo. They suggest that the extent of suppression of tyrosine kinase activity by CI-1033, rather than the baseline activity level before treatment, may predict for ultimate treatment efficacy. They also confirm the capacity of CI-1033 to enhance radiation response (particularly in vivo) as has been identified for several other epidermal growth factor receptor (EGFR) inhibitors. Nyati et al. also suggest that selected downstream signaling mols. of the EGFR pathway may serve as candidate markers for predicting response to ErbB inhibition.

IT **289499-45-2**, CI-1033
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization by EGFR inhibitor CI-1033: searching for reliable EGFR response predictors)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41317 CAPLUS
DOCUMENT NUMBER: 140:99649
TITLE: Pharmaceutical compositions for the treatment of respiratory tract diseases comprising novel anticholinergic agents and inhibitors of EGFR-kinase
INVENTOR(S): Pairet, Michel; Meade, Christopher John Montague; Pieper, Michael P.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Gmbh & Co. Kg, Germany

10/ 023,099

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

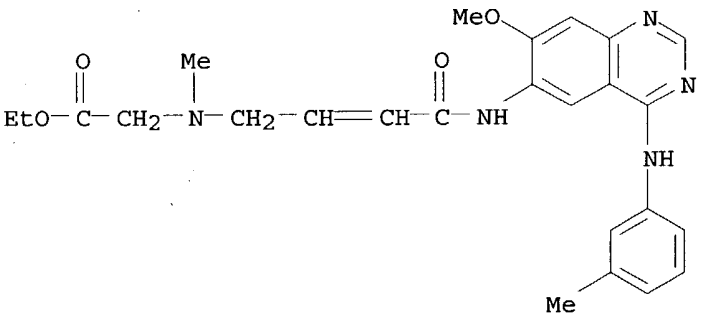
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004775	A1	20040115	WO 2003-EP6788	20030626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10230751	A1	20040122	DE 2002-10230751	20020709
US 2004048887	A1	20040311	US 2003-614382	20030707
PRIORITY APPLN. INFO.:			DE 2002-10230751 A	20020709
			US 2002-407746P P	20020903

OTHER SOURCE(S): MARPAT 140:99649

AB The invention relates to novel pharmaceutical compns. comprising novel anticholinergic agents and EGFR-kinase inhibitors, method for production and use thereof in the treatment of respiratory diseases. The synthesis of several EGFR-kinase inhibitors is given. Thus an inhalation capsule contained (microgram/capsule): 2,2-Diphenylpropionic acid scopine ester methobromide 60; EGFR kinase inhibitor 3500; lactose 3440.

IT **290301-86-9P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. for treatment of respiratory tract diseases comprising anticholinergic agents and inhibitors of EGFR-kinase)

RN 290301-86-9 CAPLUS
CN Glycine, N-[4-[[7-methoxy-4-[(3-methylphenyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:41213 CAPLUS
DOCUMENT NUMBER: 140:105249
TITLE: Combination of mTOR inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms
INVENTOR(S): Neel, Benjamin G.; Mohi, Golam

10/ 023,099

PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004644	A2	20040115	WO 2003-US20972	20030703
WO 2004004644	A3	20040506		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

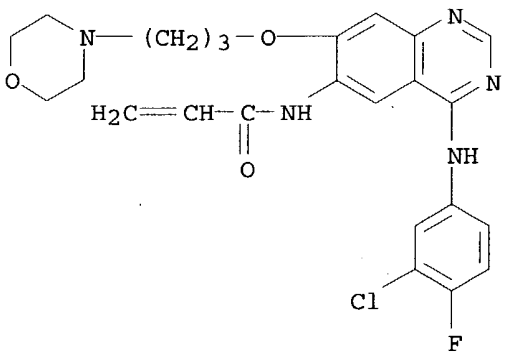
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-394029P P 20020705
US 2002-412402P P 20020920

AB The invention features methods and compns. including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of mTOR inhibitor and tyrosine kinase inhibitor for cancer therapy)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 23 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:1000449 CAPLUS
DOCUMENT NUMBER: 140:35213

10/ 023,099

TITLE: CI-1033, an irreversible pan-erbB receptor inhibitor and its potential application for the treatment of breast cancer

AUTHOR(S): Allen, Lee F.; Eiseman, Irene A.; Fry, David W.; Lenehan, Peter F.

CORPORATE SOURCE: Departments of Clinical Development, Oncology and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, MI, USA

SOURCE: Seminars in Oncology (2003), 30(5, Suppl. 16), 65-78
CODEN: SOLGAV; ISSN: 0093-7754

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal; General Review

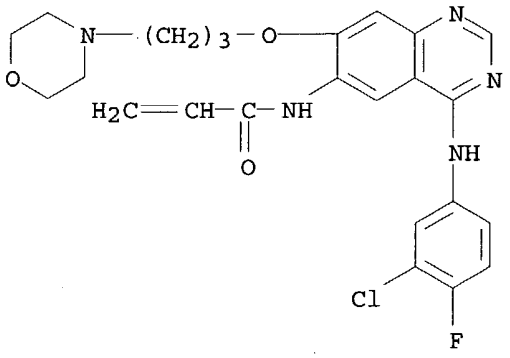
LANGUAGE: English

AB A review. The erbB family of cell surface receptor proteins consists of four members, all of which play a role in the development and growth of the normal breast. The activity of this signaling pathway is normally tightly controlled, and dysregulation has been shown to play a significant role in the pathogenesis and progression of breast and other cancers. The potent transforming potential of these receptors is further enhanced by the coexpression of multiple members of this receptor family, which worsens prognosis. Therapeutic blockade of erbB-2 receptor signaling has to date been shown to be effective in only a subset of chemotherapy-resistant breast cancer patients. CI-1033 is a highly potent and selective pan-erbB inhibitor that efficiently blocks signal transduction through all four members of the erbB receptor family. In addition, it covalently binds to these receptors, irreversibility inhibiting them, and thereby provides for prolonged suppression of erbB receptor-mediated signaling. Clin., it has been shown to have an acceptable side effect profile at potentially therapeutic doses and schedules. Biomarker studies have shown target inhibition in patients, and evidence of antitumor activity has also been observed in phase I studies. Given the broad expression pattern of the erbB family of receptors in solid tumors, and the important proliferative effect of co-expression of multiple erbB receptors, CI-1033, as an irreversible, pan-erbB inhibitor, has the potential to have an important role in the future treatment of breast and other cancers.

IT **289499-45-2**, CI-1033
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potential use of pan-erbB receptor inhibitor CI-1033 for treatment of breast cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:991352 CAPLUS
DOCUMENT NUMBER: 140:23228
TITLE: Method of treating cancer using kinase inhibitors
INVENTOR(S): Agus, David B.
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003103676	A2	20031218	WO 2003-US17565	20030604
WO 2003103676	A3	20040325		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004001833	A1	20040101	US 2003-454323	20030604
PRIORITY APPLN. INFO.:			US 2002-386622P P	20020605

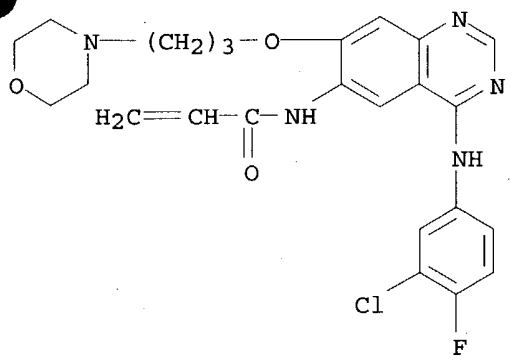
AB Described herein are methods for treating cancer and other disease conditions in individuals who have either developed a resistance to conventional tyrosine kinase inhibitor (TKI) therapy or who are non-responsive ab initio to conventional TKI therapy. In various embodiments, the methods include administering to a patient a resistance-surmounting quantity of a TKI on a weekly or semi-weekly basis. Alternate embodiments of the present invention include a diagnostic method for assessing an individual's probability of being resistant to TKI therapy, based upon an expression level of epithelial membrane protein-1 (EMP-1); one of the genes believed to be responsible for TKI resistance.

The methods of the present invention may be particularly useful in the treatment of lung, breast, prostate, ovarian, brain and colon cancers. The methods of the present invention may be effective in blocking the HER-2 kinase domain either in addition to or in lieu of blocking the EGFR kinase domain.

IT **289499-45-2**, CI1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of cancer using inhibitors of tyrosine kinase)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 25 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:971922 CAPLUS
DOCUMENT NUMBER: 140:23220
TITLE: Preventives and/or remedies for subjects with the expression or activation of her2 and/or EGFR
INVENTOR(S): Suzuki, Tsuyoshi; Kitano, Yasunori; Yano, Shinji
PATENT ASSIGNEE(S): Mitsubishi Pharma Corporation, Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101491	A1	20031211	WO 2003-JP6988	20030603

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2002-162130 A 20020603

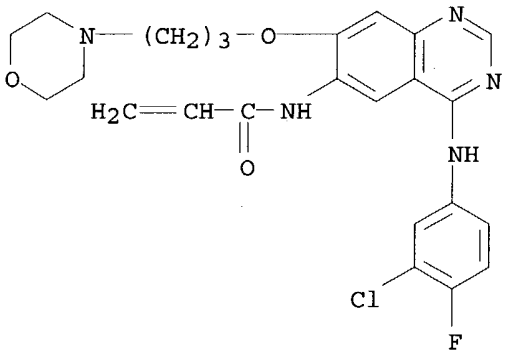
OTHER SOURCE(S): MARPAT 140:23220

AB Her2 and/or EGFR inhibitors to be administered to subjects with the overexpression or activation of Her2 and/or EGFR that have been subjected to an examination for detecting the expression or activity of Her2 and/or EGFR and thus regarded as having the overexpression or activation of Her and/or EGFR; and medicinal compns. containing such an inhibitor.

IT **267243-28-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazoline analogs as preventives and/or remedies for subjects with the expression or activation of her2 and/or EGFR)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:931201 CAPLUS

DOCUMENT NUMBER: 140:13024

TITLE: EGF receptor antagonists in the treatment of gastric cancer

INVENTOR(S): Luber, Birgit; Fuchs, Margit Roswitha; Hoefler, Heinz; Fend, Falko; Gamboa-Dominguez, Armando

PATENT ASSIGNEE(S): Technische Universitaet Muenchen, Germany

SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097086	A2	20031127	WO 2003-EP5057	20030514
WO 2003097086	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

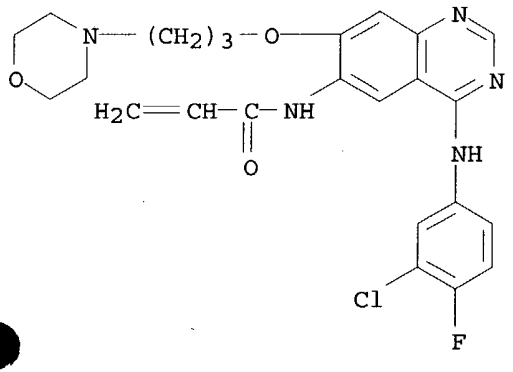
PRIORITY APPLN. INFO.: US 2002-380285P P 20020515
EP 2003-4524 A 20030228

AB The invention relates to a use of (an) EGF receptor antagonist(s)/inhibitor(s) for the preparation of a pharmaceutical composition for the prevention, amelioration or treatment of gastric carcinomas, preferably for the prevention, amelioration or treatment of diffuse gastric carcinomas. Furthermore, the invention provides for a method for treating or for preventing gastric carcinomas, in particular diffuse gastric carcinomas comprising the administration of at least one EGF receptor antagonist/inhibitor to a subject in need of such a treatment or prevention.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGF receptor antagonists in treatment of gastric cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 27 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:913005 CAPLUS
DOCUMENT NUMBER: 139:391384
TITLE: Use of inhibitors of EGFR-mediated signal transduction for the treatment of benign prostatic hyperplasia (BPH)/prostatic hypertrophy
INVENTOR(S): Singer, Thomas; Colbatzky, Florian; Platz, Stefan
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003094921	A2	20031120	WO 2003-EP4606	20030502
WO 2003094921	A3	20040318		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

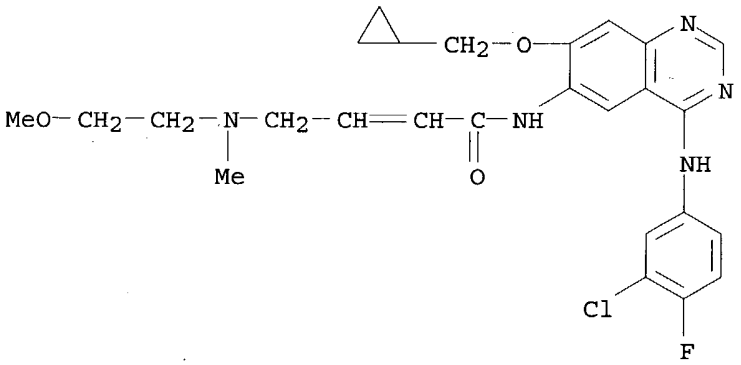
DE 10221018	A1	20031127	DE 2002-10221018	20020511
US 2003225079	A1	20031204	US 2003-431699	20030508
PRIORITY APPLN. INFO.:			DE 2002-10221018	A 20020511
			US 2002-389815P	P 20020618

OTHER SOURCE(S): MARPAT 139:391384

AB The invention discloses the use of EGF-receptor antagonists for the production of a medicament to prevent and/or treat benign prostatic hyperplasia and/or prostatic hypertrophy, as well as a method for the treatment or prevention of benign prostatic hyperplasia/prostatic hypertrophy involving the administration of an EGF-receptor antagonist, optionally in combination with known compds. for the treatment of benign prostatic hyperplasia/prostatic hypertrophy, and the corresponding pharmaceutical compns. Compds. of the invention include e.g. quinazoline derivs. and monoclonal antibodies. Preparation of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(N-(2-methoxyethyl)-N-methylamino)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline is described.

IT **439081-48-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EGFR-mediated signal transduction inhibitors for treatment of benign prostatic hyperplasia/prostatic hypertrophy)

RN 439081-48-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2-methoxyethyl)methylamino]- (9CI) (CA INDEX NAME)



L3 ANSWER 28 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:892616 CAPLUS
DOCUMENT NUMBER:	139:358814
TITLE:	Methods for the treatment of glaucoma and other conditions mediated by NOS-2 expression via inhibition of the EGFR pathway
INVENTOR(S):	Liu, Bin; Neufeld, Arthur H.
PATENT ASSIGNEE(S):	Washington University, USA
SOURCE:	PCT Int. Appl., 52 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English

10/ 023,099

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

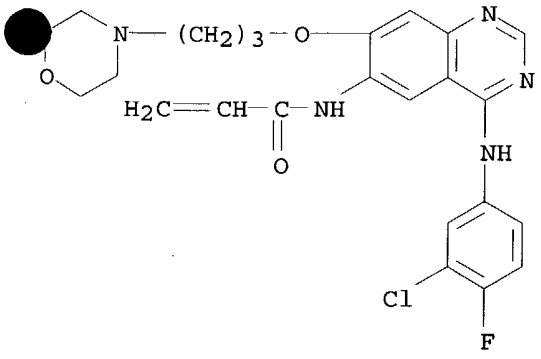
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092693	A1	20031113	WO 2003-US14484	20030506
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003232741	A1	20031218	US 2003-430527	20030506
PRIORITY APPLN. INFO.:			US 2002-378254P P	20020506

AB Therapeutic methods and compns. for the treatment of glaucoma and other conditions mediated at least in part by the expression of NOS-2 are provided.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treatment of glaucoma and other conditions mediated by NOS-2 expression via inhibition of EGFR pathway)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

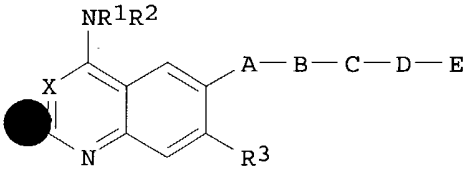
L3 ANSWER 29 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:855936 CAPLUS
DOCUMENT NUMBER: 139:350749
TITLE: Preparation of 4-aminoquinazolines as inhibitors of epidermal growth factor receptor (EGF-R)
INVENTOR(S): Himmelsbach, Frank; Jung, Birgit; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 56 pp.

10/ 023,099

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003089439	A1	20031030	WO 2003-EP3828	20030414
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10217689	A1	20031113	DE 2002-10217689	20020419
US 2004044014	A1	20040304	US 2003-417647	20030417
PRIORITY APPLN. INFO.:			DE 2002-10217689 A	20020419
			US 2002-387021P P	20020607

OTHER SOURCE(S): MARPAT 139:350749
GI



I

AB Title compds. [I; R1 = H, alkyl; R2 = Ph, benzyl, 1-phenylethyl in which Ph is substituted; R3 = H, F, Cl, Br, OH, alkoxy, fluorinated OMe, OEt, substituted alkoxy; cycloalkyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, etc.; A = imino, alkylimino, B = CO, SO2; C = (substituted) 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, C.tplbond.CH, etc.; D = (branched) alkylene; E = bridged pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl] tautomers, stereoisomers, mixts. and salts thereof, particularly their physiol. compatible salts with inorg. or organic acids, were prepared Thus, a solution of LiCl in H2O was treated with 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-(diethoxyphosphoryl)acetylamino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline (preparation given) in THF followed by addition of KOH-pellets and cooling at -3°. Then, the reaction mixture was dropwise treated with (1S,4S)-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)acetaldehyde hydrochloride (preparation given) for 5 min at 0° followed by stirring for 10 min at 0° and for 20 min at room temperature to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-1-oxo-2-buten-1-yl)amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline. The latter inhibited EGF-receptor kinase with IC50 = 0.5 nM. The invention also relates to the use of these compds. for treating diseases, particularly tumor diseases and benign prostatic hyperplasia (BPH), diseases of the lungs and of the respiratory tract.

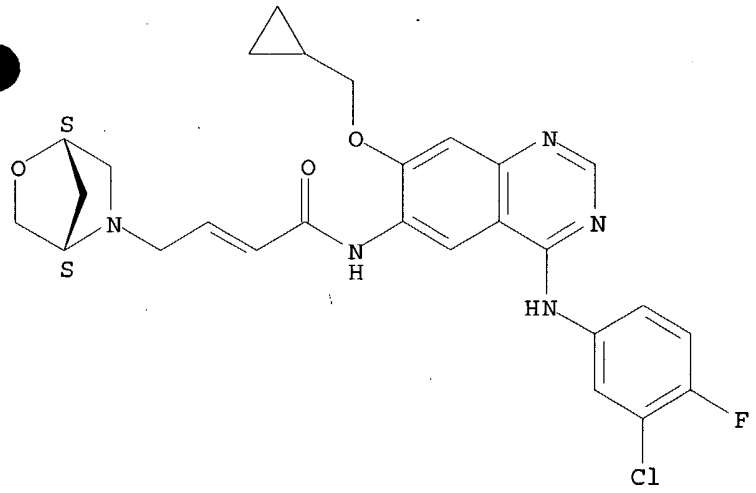
IT **618061-81-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoquinazolines as inhibitors of epidermal growth factor receptor (EGF-R))

RN 618061-81-7 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:656610 CAPLUS
DOCUMENT NUMBER: 139:202486
TITLE: Inhalants containing anticholinergic agents and EGFR kinase inhibitors
INVENTOR(S): Jung, Birgit; Pairet, Michel; Pieper, Michael P.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068264	A1	20030821	WO 2003-EP1357	20030212

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10206505	A1	20030828	DE 2002-10206505		20020216
US 2003158196	A1	20030821	US 2003-360064		20030207
EP 1478398	A1	20041124	EP 2003-704593		20030212

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

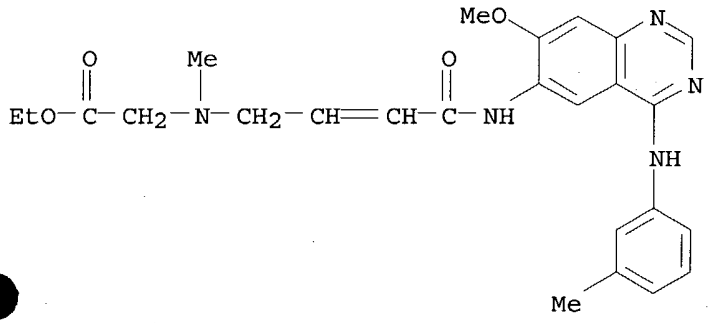
PRIORITY APPLN. INFO.:	DE 2002-10206505	A	20020216
	US 2002-369213P	P	20020401
	WO 2003-EP1357	W	20030212

AB The invention relates to novel medicinal compns. on the basis of anticholinergic agents and EGFR kinase inhibitors, methods for their production and their use for treating respiratory diseases. Thus a series of quinazoline derivs. were synthesized that were EGFR kinase inhibitors. A typical inhalation powder contained (μg/capsule): tiotropium bromide 10.8; EGFR kinase inhibitor 3500; lactose 3489.2.

IT **290301-86-9P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhalants containing anticholinergic agents and EGFR kinase inhibitors)

RN 290301-86-9 CAPLUS

CN Glycine, N-[4-[[7-methoxy-4-[(3-methylphenyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:633416 CAPLUS
DOCUMENT NUMBER:	139:173786
TITLE:	Method for treating diseases associated with abnormal kinase activity
INVENTOR(S):	Lyons, John; Rubinfeld, Joseph
PATENT ASSIGNEE(S):	Supergen, Inc., USA
SOURCE:	PCT Int. Appl., 64 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003065995	A2	20030814	WO 2003-US3537	20030206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

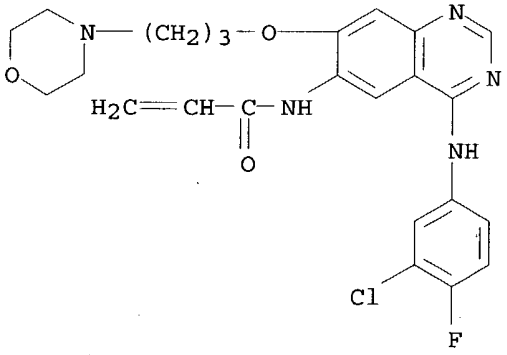
US 2003147813	A1	20030807	US 2002-71849	20020207
US 2004127453	A1	20040701	US 2002-206854	20020726
PRIORITY APPLN. INFO.:			US 2002-71849	A1 20020207
			US 2002-206854	A1 20020726

AB Methods are provided for treating diseases associated with abnormal activity of kinases such as chronic myelogenous leukemia. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amount; and administering a kinase inhibitor such as imatinib mesylate to the patient in therapeutically effective amount, such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat cancer associated with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (P13K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor family (FGFR) insulin receptor family, ephrin receptor family, Met family, Ror family, c-kit family, Src family, Fes family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Abl family.

IT **289499-45-2**, CI1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of diseases associated with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 32 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:607455 CAPLUS
DOCUMENT NUMBER:	139:159940
TITLE:	Use of tyrosine kinase inhibitors for treatment of pulmonary inflammatory conditions
INVENTOR(S):	Jung, Birgit; Puschner, Hubert
PATENT ASSIGNEE(S):	Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany

10/ 023,099

SOURCE: Ger. Offen., 24 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10204462	A1	20030807	DE 2002-10204462	20020205
WO 2003066060	A2	20030814	WO 2003-EP814	20030128
WO 2003066060	A3	20040115		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1474149	A2	20041110	EP 2003-704477	20030128
US 2003149062	A1	20030807	US 2003-353616	20030129

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

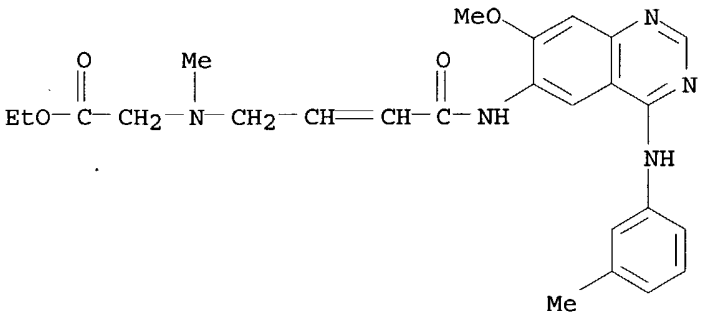
PRIORITY APPLN. INFO.:	DE 2002-10204462	A	20020205
	WO 2003-EP814	W	20030128

OTHER SOURCE(S): MARPAT 139:159940

AB The invention discloses the use of quinazoline derivs. (Markush included), or the compds. (1) 4-[(3-chloro-4-fluorphenyl)amino]-6-[(4-dimethylaminocyclohexyl)amino]pyrimido[5,4-d]pyrimidine; (2) 4-[(R)-(1-phenylethyl)amino]-6-(4-hydroxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine; (3) 4-[(3-Chloro-4-(3-fluoro-4-benzyloxy)phenyl)amino]-6-[5-(((2-methansulfonylethyl)amino)methyl)-furan-2-yl]quinazoline; or the antibody cetuximab C225, trastuzumab, ABX-EGF, Mab ICR-62 and EGFR antisense, their tautomers, their stereoisomers and their salts, in particular their physiol. compatible salts with inorg. or organic acids or bases, for the production of a medication for prevention or treatment of diseases of the respiratory system or the lung. Preparation of quinazoline compds. is included.

IT **290301-86-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tyrosine kinase inhibitors for treatment of pulmonary inflammatory conditions)

RN 290301-86-9 CAPLUS
CN Glycine, N-[4-[[7-methoxy-4-[(3-methylphenyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)



L3 ANSWER 33 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

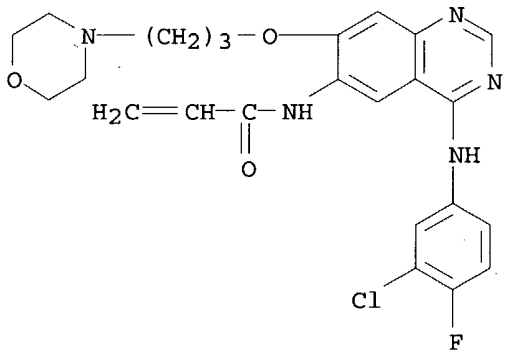
ACCESSION NUMBER: 2003:355612 CAPLUS
DOCUMENT NUMBER: 138:362649
TITLE: Treatment of cancer with anti-ErbB2 antibodies
INVENTOR(S): Sliwkowski, Mark X.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. Ser. No. 602,812.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003086924	A1	20030508	US 2002-268501		20021010
US 2004013667	A1	20040122	US 2003-608626		20030627
PRIORITY APPLN. INFO.:			US 1999-141316P	P	19990625
			US 2000-602812	A2	20000623
			US 2002-268501	A2	20021010

AB The present application describes methods for treating cancer with anti-ErbB2 antibodies, such as anti-ErbB2 antibodies that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal antibody 2C4 was effective in inhibiting breast cancer tumor growth in MCF7 xenografts.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as tyrosine kinase inhibitor in combination with anti-ErbB2 antibodies; cancer treatment with anti-ErbB2 antibodies)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 34 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:300894 CAPLUS
DOCUMENT NUMBER: 138:297633
TITLE: Method of treatment of thyroid cancer
INVENTOR(S): Fagin, James Alexander
PATENT ASSIGNEE(S): The University of Cincinnati, USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

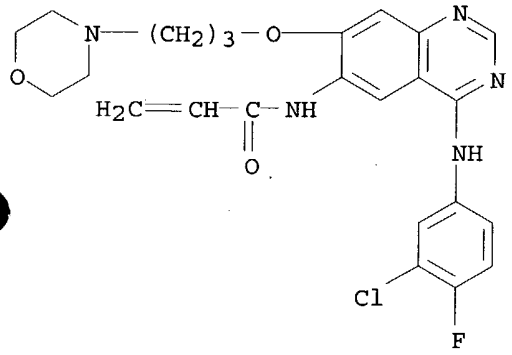
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003030908	A2	20030417	WO 2002-US32195	20021008
WO 2003030908	A3	20031106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1435959	A2	20040714	EP 2002-778482	20021008
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004191254	A1	20040930	US 2004-491859	20040407
PRIORITY APPLN. INFO.:			US 2001-327880P	P 20011009
			WO 2002-US32195	W 20021008

AB The invention relates to a method of treating a warm-blooded animal, especially a human, having a disease which is mediated or characterized by mutations in the RET gene, or thyroid cancer, especially thyroid cancer harboring RET mutations, comprising administering to said animal a therapeutically effective amount of a compound which decreases the activity of the epidermal growth factor (EGF), especially a compound as defined herein.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

10/ 023,099

(treatment of thyroid cancer)
RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 35 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:154278 CAPLUS
DOCUMENT NUMBER: 138:198670
TITLE: GnRh agonist combination drugs
INVENTOR(S): Furuya, Shuichi; Kusaka, Masami
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015820	A1	20030227	WO 2002-JP8130	20020808
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003137814	A2	20030514	JP 2002-231922	20020808
EP 1424080	A1	20040602	EP 2002-758814	20020808
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.: JP 2001-244616 A 20010810
WO 2002-JP8130 W 20020808

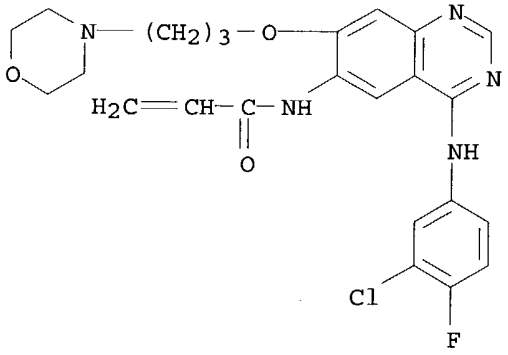
AB In the field of pharmaceuticals, it is intended to provide drugs whereby the preventive and therapeutic effects of a GnRH agonist on various diseases can be enhanced and QOL can be improved. More specifically, combination drugs characterized in that the GnRH agonist is combined with

a chemical selected from among SERM, SARM, sex hormone synthesis inhibitors, receptor-type tyrosine kinase inhibitors, bone metabolism regulators, drugs for immunotherapy, cytokine/chemokine inhibitors and endothelin receptor antagonists. Owing to these combinations, excellent effects of enhancing the preventive and therapeutic effects of the GnRH agonist on various diseases and relieving side effects can be established. Furthermore, QOL can be improved thereby.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GnRH agonist combination drugs for treating various diseases and relieving side effects)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 36 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:8967 CAPLUS
DOCUMENT NUMBER: 139:62338
TITLE: Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents
AUTHOR(S): Laird, A. Douglas; Cherrington, Julie M.
CORPORATE SOURCE: SUGEN, Inc., South San Francisco, CA, 94080, USA
SOURCE: Expert Opinion on Investigational Drugs (2003), 12(1), 51-64
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

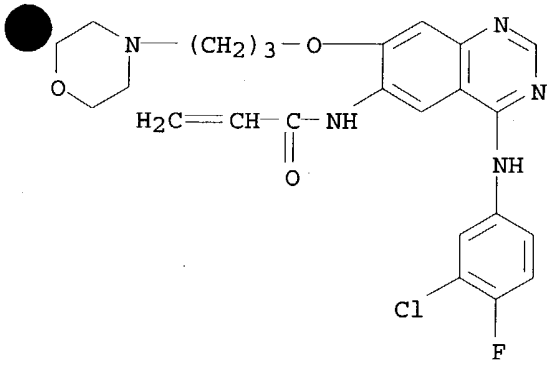
AB A review. Numerous small mol. synthetic tyrosine kinase inhibitors are in clin. development for the treatment of human cancers. These fall into three broad categories: inhibitors of the epidermal growth factor receptor tyrosine kinase family (e.g., Iressa and Tarceva), inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248) and inhibitors of tyrosine kinases from multiple subgroups (e.g., Gleevec). In addition, agents targeting other tyrosine kinases implicated in cancer, such as Met, Tie-2 and Src, are in preclin. development. As experience is gained in the clinic, it has become clear that unleashing the full therapeutic potential of tyrosine kinase

inhibitors will require patient preselection, better assays to guide dose selection, knowledge of mechanism-based side effects and ways to predict and overcome drug resistance.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small mol. tyrosine kinase inhibitors and clin. development of anticancer agents)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 37 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:974164 CAPLUS

DOCUMENT NUMBER: 139:143003

TITLE: Clinical evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer

AUTHOR(S): Lin, Edward H.; Abbruzzese, James L.

CORPORATE SOURCE: Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

SOURCE: Oncogene-Directed Therapies (2003), 313-330. Editor(s): Rak, Janusz. Humana Press Inc.: Totowa, N. J. CODEN: 69DKTX; ISBN: 0-89603-982-X

DOCUMENT TYPE: Conference; General Review

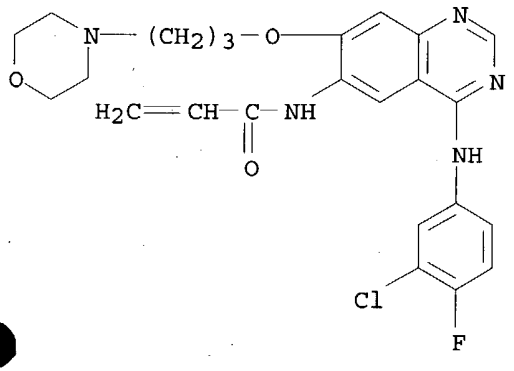
LANGUAGE: English

AB A review. Proteins encoded by oncogenes and tumor-suppressor genes are the essential signaling components of the complex cellular signaling networks. Cancer arises from a multi-step process promoted by the imbalanced growth signals as a consequence of gain of oncogene and/or loss of tumor suppressor genes. The six essential cancer hallmarks include persistent cell growth signals, insensitivity to anti-growth signals, evasion of apoptosis, persistent angiogenesis, gain of cell immortality, and tumor invasion and metastasis. As an oncogene, gain of epidermal growth factor receptor (EGFR) function is achieved through EGFR over-expression and has been shown to be associated with almost all the six essential hallmarks of cancer except the gain of cell immortality. In

various exptl. models, EGFR inhibition leads to regression of tumor cell growth, inhibition of angiogenesis, induction of apoptosis, and inhibition of tumor invasion and metastasis. Furthermore, over-expression of EGFR, frequently observed in a number of human cancers, is associated with poor overall prognosis, increased tumor recurrence, and decreased patient survival. The hypothesis that EGFR might be a cancer therapeutic target was proposed by Mendelsohn in the early 1980s; emerging only recently are the promising clin. trial results from a number of EGFR antagonists in different human cancers. This review will discuss the clin. developments and future directions of EGFR antagonists in cancer treatment.

IT **289499-45-2**, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 135 THERE ARE 135 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 38 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:651435 CAPLUS
DOCUMENT NUMBER: 138:180074
TITLE: Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer
AUTHOR(S): Allen, Lee F.; Lenehan, Peter F.; Eiseman, Irene A.; Elliott, William L.; Fry, David W.
CORPORATE SOURCE: Departments of Clinical Development, Oncology, and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor, MI, USA
SOURCE: Seminars in Oncology (2002), 29(3, Suppl. 11), 11-21
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

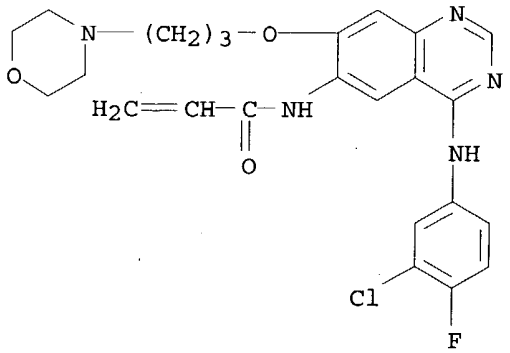
AB A review. Transmembrane receptor Tyr kinases were shown to play an important role in the modulation of growth factor signaling and regulation of key cellular processes. The erbB receptor family is part of the receptor Tyr kinase superfamily and consists of 4 members, erbB-1, erbB-2,

erbB-3, and erbB-4. A majority of solid tumors express 1 or more members of this receptor family, and coexpression of multiple erbB receptors leads to an enhanced transforming potential and worsened prognosis. The erbB receptor family was shown to play an important role in both the development of the normal breast and in the pathogenesis and progression of breast cancer. Receptor overexpression was also shown to be a neg. prognostic indicator and to correlate with both tumor invasiveness and a lack of responsiveness to standard treatment. Clin., blockade of the erbB-2 receptor has recently been shown to provide benefit in a subset of chemotherapy-resistant breast cancer patients. CI-1033 is an orally available pan-erbB receptor Tyr kinase inhibitor that, unlike the majority of receptor inhibitors, effectively blocks signal transduction through all 4 members of the erbB family. In addition, it blocks the highly tumorigenic, constitutively activated variant of erbB-I, EGFRvIII, and inhibits downstream signaling through both the Ras/MAP kinase, and PI-3 kinase/AKT pathways. CI-1033 is also unique in that it is an irreversible inhibitor, thereby providing prolonged suppression of erbB receptor-mediated signaling. Preclin. data have shown CI-1033 to be efficacious against a variety of human tumors in mouse xenograft models, including breast carcinomas. In a phase I study, CI-1033 was shown to have an acceptable side effect profile at potentially therapeutic dose levels and demonstrates evidence of target biomarker modulation. Antitumor activity was also observed in this study, including 1 partial clin. response and stable disease in over 30% of patients, including 1 patient with heavily pretreated breast cancer. By virtue of its pan-erbB receptor inhibition and potent interruption of downstream mitogenic signaling pathways, CI-1033 may have clin. activity for solid tumors that overexpress 1 erbB family member, coexpress multiple members of the erbB family, or express a constitutively activated, mutated form of these receptors. Given the important role of the erbB receptor family in the pathogenesis and progression of breast cancer, an irreversible pan-erbB inhibitor like CI-1033 could have an important role to play in the future treatment of breast cancer.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1033 in treatment of breast cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

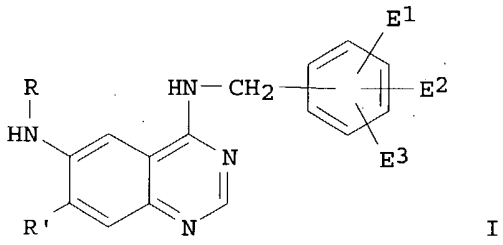
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR

THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 39 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:610316 CAPLUS
DOCUMENT NUMBER: 137:163829
TITLE: Use of a composition comprising a retinoid and an Erb inhibitor in the preparation of a medicament for the treatment of retinoid skin damage
INVENTOR(S): Elder, James Tilford; Varani, James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1230919	A2	20020814	EP 2002-2611	20020205
EP 1230919	A3	20021218		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NZ 516873	A	20031128	NZ 2002-516873	20020128
CA 2370236	AA	20020812	CA 2002-2370236	20020131
AU 2002015470	A5	20020815	AU 2002-15470	20020207
CN 1370535	A	20020925	CN 2002-104570	20020208
US 2002169176	A1	20021114	US 2002-73569	20020211
ZA 2002001157	A	20030811	ZA 2002-1157	20020211
JP 2002275095	A2	20020925	JP 2002-33608	20020212
US 2004198752	A1	20041007	US 2004-824182	20040414
PRIORITY APPLN. INFO.:			US 2001-268220P	P 20010212
			US 2002-73569	A1 20020211

OTHER SOURCE(S): MARPAT 137:163829
GI

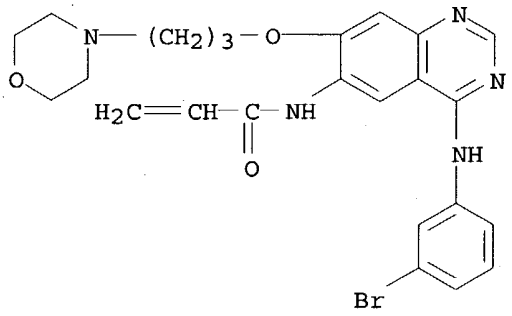


I

AB Erb inhibitors used in combination with retinoids are effective to prevent skin injury otherwise caused by retinoids alone. A method of treating skin aging and similar skin disorders comprises administering retinoids in combination with erb inhibitors I (E1-E3 include halo; R is alkylcarbonyl or alkenylcarbonyl; R' is lower alkoxy optionally substituted with amino groups).

IT **198959-99-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retinoid and Erb inhibitor for treatment of retinoid skin damage)

RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

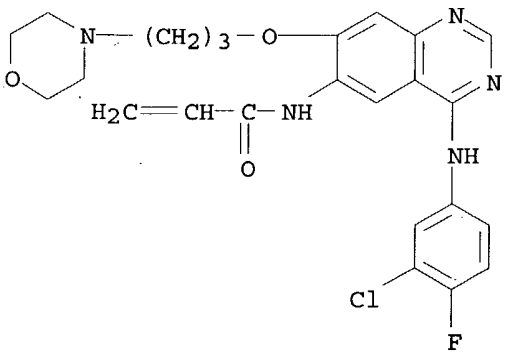


L3 ANSWER 40 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:604225 CAPLUS
DOCUMENT NUMBER: 138:162767
TITLE: EGF signal transduction and its molecular targeted drugs against cancer
AUTHOR(S): Sone, Saburo; Yamamoto, Akihiko
CORPORATE SOURCE: Dep. Internal Med. Molecular Therapeutics, Univ. Tokushima Sch. Med., Japan
SOURCE: Saishin Igaku (2002), 57(7), 1712-1717
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. The epidermal growth factor receptor (EGFR) and its inhibition in cancer therapy is reviewed together with the mechanism related to EGF signal transduction of antitumor agents such as EGFR antibody (C225) and EGFR tyrosine kinase inhibitors (ZD1839, OSI-774, and CI-1033).

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGF signal transduction and its mol. targeted drugs against cancer)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

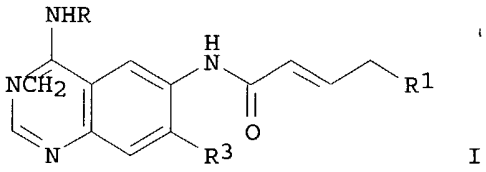


●2 HCl

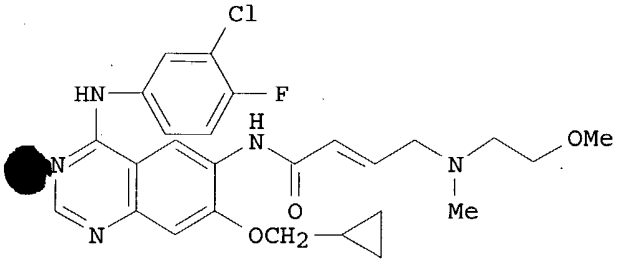
L3 ANSWER 41 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:487536 CAPLUS
DOCUMENT NUMBER: 137:63250
TITLE: Quinazoline derivatives as inhibitors of human EFG tyrosine kinase
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Blech, Stefan; Jung, Birgit; Baum, Elke; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002050043	A1	20020627	WO 2001-EP14569		20011212
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
DE 10063435	A1	20020704	DE 2000-10063435		20001220
CA 2432428	AA	20020627	CA 2001-2432428		20011212
AU 2002019174	A5	20020701	AU 2002-19174		20011212
EP 1345910	A1	20030924	EP 2001-271363		20011212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
EE 200300300	A	20031015	EE 2003-300		20011212
BR 2001016266	A	20040217	BR 2001-16266		20011212
JP 2004516283	T2	20040603	JP 2002-551540		20011212
US 2002173509	A1	20021121	US 2001-23099		20011217
ZA 2003004141	A	20040415	ZA 2003-4141		20030528
NO 2003002726	A	20030616	NO 2003-2726		20030616
PRIORITY APPLN. INFO.:			DE 2000-10063435	A	20001220
			US 2000-259201P	P	20001228
			WO 2001-EP14569	W	20011212

OTHER SOURCE(S): MARPAT 137:63250
GI



I



II

AB Quinazoline derivs. I [R = PhCH2, PhCHMe, 3,4-Cl(F)C6H3; R1 = NMeR2, NEt2, NEtCH2CH2OMe, N(CH2CH2OMe)2, morpholino; R2 = Me, Et, CHMe2, cyclopropyl, CH2CH2OMe, 3-tetrahydrofuryl, 2-tetrahydrofurylmethyl, 3-tetrahydrofurylmethyl, 4-tetrahydropyranyl, 4-tetrahydropyranylmethyl; R3 = cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, 3-tetrahydrofuranyloxy, 2-tetrahydrofuranylmethoxy, 3-tetrahydrofuranylmethoxy, 4-tetrahydropyranyloxy, 4-tetrahydropyranylmethoxy] were prepared for use as inhibitors of signal transduction caused by human EFG receptor tyrosine kinase. They are useful in the treatment of tumoral diseases, diseases of the lung and the respiratory tract, the gastrointestinal tract, and the gallbladder and bile ducts. Thus, the quinazoline II was prepared by converting bromocrotonic acid to its chloride, and reaction with 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline, followed by MeNHCH2CH2OMe. II had an IC50 against human EFG receptor kinase of 0.7 nM.

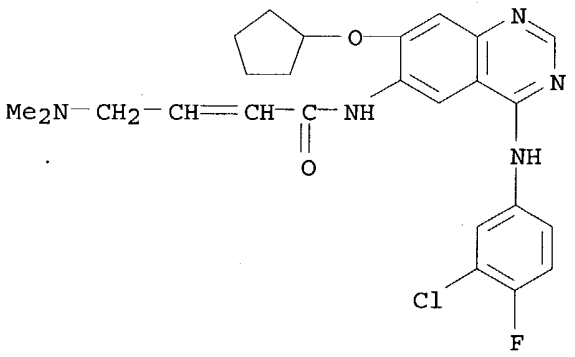
IT **439081-10-4P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

RN 439081-10-4 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



10/ 023,099

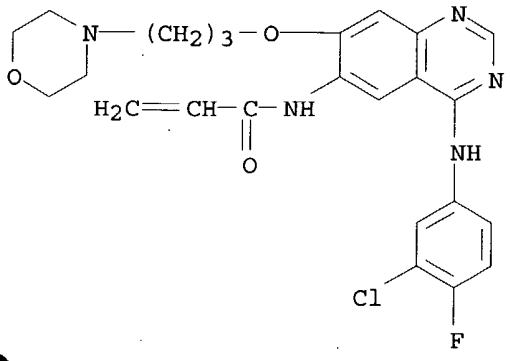
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 42 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:414301 CAPLUS
DOCUMENT NUMBER: 138:32893
TITLE: Drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases: implications for cancer therapy
AUTHOR(S): Citri, Ami; Alroy, Iris; Lavi, Sara; Rubin, Chanan; Xu, Wanping; Grammatikakis, Nicolas; Patterson, Cam; Neckers, Len; Fry, David W.; Yarden, Yosef
CORPORATE SOURCE: Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: EMBO Journal (2002), 21(10), 2407-2417
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Overexpression of ErbB-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clin. application. Tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the kinase are especially effective against tumors. Here the authors report an unexpected activity of TKIs: along with inhibition of tyrosine phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of ErbB-2 mols. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to ErbB receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein 90 (Hsp90) antagonist geldanamycin and a stress-induced mechanism. In agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of ErbB-2, the authors propose a general strategy for selective destruction of oncoproteins by targeting their interaction with mol. chaperones.

IT **289499-45-2**, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases and implications for cancer therapy with tyrosine kinase inhibitors and Hsp90 antagonist geldanamycin)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

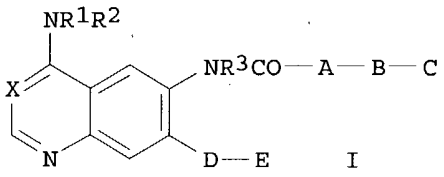
L3 ANSWER 43 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:171892 CAPLUS
DOCUMENT NUMBER: 136:216762
TITLE: Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018376	A1	20020307	WO 2001-EP9536	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10042062	A1	20020307	DE 2000-10042062	20000826
AU 2001095482	A5	20020313	AU 2001-95482	20010818
CA 2417907	AA	20030130	CA 2001-2417907	20010818
EP 1315720	A1	20030604	EP 2001-976108	20010818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004507538	T2	20040311	JP 2002-523891	20010818
US 2002115675	A1	20020822	US 2001-934631	20010822
US 6740651	B2	20040525		

PRIORITY APPLN. INFO.:

DE 2000-10042062	A	20000826
US 2000-230542P	P	20000905
WO 2001-EP9536	W	20010818

OTHER SOURCE(S): MARPAT 136:216762
GI



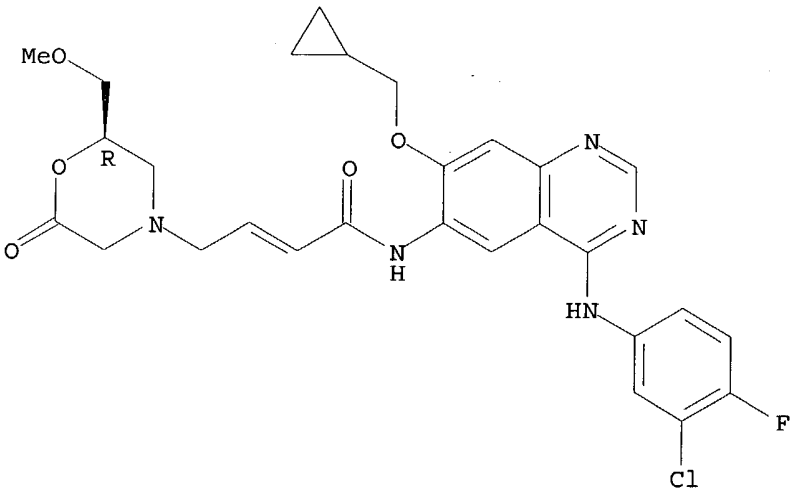
I

AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = (substituted) alkenyl, alkenylcarbonyl, etc.; C = (substituted) 2-oxomorpholin-4-yl, etc; D = oxyalkenyl, O; E = (substituted) amino, alkenylimino, imidazolyl, cycloalkyl; or DE = H, (substituted) alkoxy, etc.], were prepared Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(ethoxycarbonylmethyl)-N-((R)-2-hydroxy-3-methoxypropyl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline (preparation given) and MeSO2OH in MeCN were stirred for 4 h under reflux to give 69% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(R)-2-methoxymethyl-6-oxomorpholin-4-yl]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 2 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402569-98-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402569-98-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R)-2-(methoxymethyl)-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

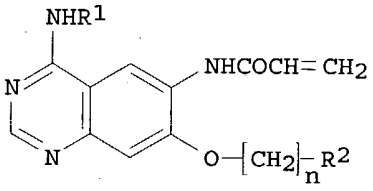
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 44 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:171891 CAPLUS
DOCUMENT NUMBER: 136:216761
TITLE: Preparation of 4-amino-6-vinylcarbonylaminoquinazoline s as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018375	A1	20020307	WO 2001-EP9534	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10042064	A1	20020307	DE 2000-10042064	20000826
AU 2002010444	A5	20020313	AU 2002-10444	20010818
CA 2417955	AA	20030130	CA 2001-2417955	20010818
EP 1322645	A2	20030702	EP 2001-978279	20010818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004507537	T2	20040311	JP 2002-523890	20010818
US 6403580	B1	20020611	US 2001-935498	20010823

PRIORITY APPLN. INFO.:
DE 2000-10042064 A 20000826
US 2000-230541P P 20000905
WO 2001-EP9534 W 20010818

OTHER SOURCE(S): MARPAT 136:216761
GI



I

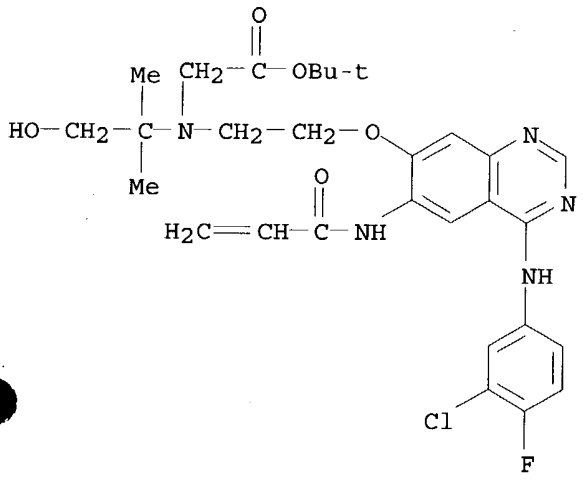
AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-(2-oxotetrahydrofuran-4-yl)methylamino, N(CH2CO2R3)2, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R3 = H, Me, Et; R4 = H, alkyl; n = 2-4],were prepared Thus, a mixture of CH2:CHCO2H and Et3N was stirred for 1 h at -50° with CH2:CHCO2Cl in THF followed by addition of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]quinazoline (preparation given) in THF at -55° and slowly heating up at 0° up to completely conversion

to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. One of the exemplified examples, 4-[(R)-(1-phenylethyl)amino]-7-[2-(2,2-dimethyl-6-oxomorpholin-4-yl)ethoxy]-6-[(vinylcarbonyl)amino]quinazoline, inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.4 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402724-13-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402724-13-4 CAPLUS

CN Glycine, N-[2-[[4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]ethyl]-N-(2-hydroxy-1,1-dimethylethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:171889 CAPLUS
DOCUMENT NUMBER: 136:232315
TITLE: Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018373	A1	20020307	WO 2001-EP9537	20010818

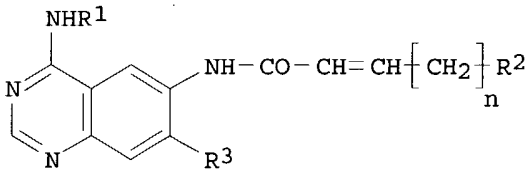
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10042060	A1	20020307	DE 2000-10042060	20000826
US 2002077330	A1	20020620	US 2001-929931	20010815
US 6653305	B2	20031125		
CA 2417050	AA	20020307	CA 2001-2417050	20010818
AU 2001084021	A5	20020313	AU 2001-84021	20010818
EP 1315717	A1	20030604	EP 2001-962953	20010818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517048	T2	20040610	JP 2002-523888	20010818

PRIORITY APPLN. INFO.:
DE 2000-10042060 A 20000826
US 2000-230389P P 20000906
WO 2001-EP9537 W 20010818

OTHER SOURCE(S): MARPAT 136:232315
GI



I

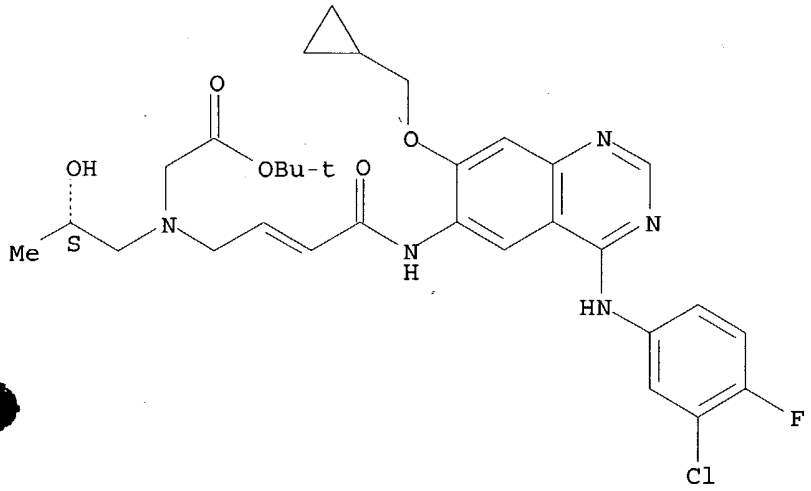
AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-[(1,3-dioxolan-2-yl)methyl]methylamino, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R4 = H, alkyl; R3 = H, (alkoxy)alkoxy, cycloalkylalkoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy; n = 1-3], were prepared Thus, a mixture of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxyquinazoline (preparation given) and diisopropylethylamine in THF was dropwise treated under ice-cooling with BrCH2CH:CHCO2Cl (preparation given) in CH2Cl2 followed by stirring for 1 h under ice-cooling and for 2 h at room temperature and addition of (S)-(2-hydroxypropylamino)acetic acid tert-Bu ester in CH2Cl2 to give after stirring over night at room temperature and stirring for 5 h at 60° 64% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(tert-butyloxycarbonylmethyl)-N-((S)-2-hydroxyprop-1-yl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. Several I inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.02-15 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402855-15-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402855-15-6 CAPLUS

CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2S)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

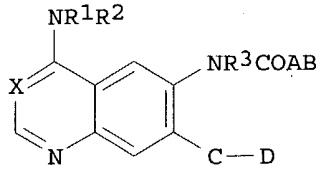
L3 ANSWER 46 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:171886 CAPLUS
DOCUMENT NUMBER: 136:216758
TITLE: Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018370	A1	20020307	WO 2001-EP9535	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10042061	A1	20020307	DE 2000-10042061	20000826
CA 2417042	AA	20020307	CA 2001-2417042	20010818
AU 2001089814	A5	20020313	AU 2001-89814	20010818
EP 1315716	A1	20030604	EP 2001-969610	20010818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004507533	T2	20040311	JP 2002-523885	20010818
US 2002082270	A1	20020627	US 2001-934753	20010822
PRIORITY APPLN. INFO.:			DE 2000-10042061 A	20000826
			US 2000-230119P P	20000905
			WO 2001-EP9535 W	20010818

OTHER SOURCE(S): MARPAT 136:216758

10/ 023,099

GI



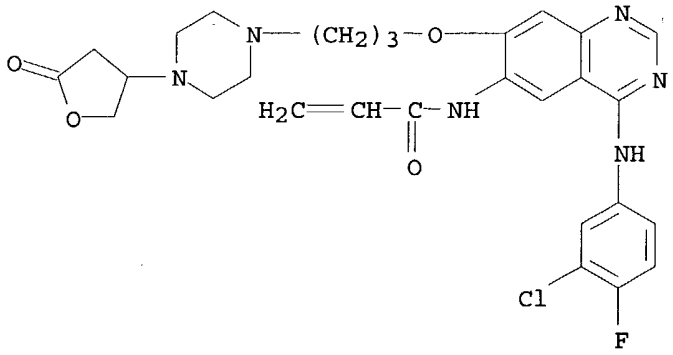
I

AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = H, (substituted) alkyl, alkylcarbonyl, CO2H, alkoxycarbonyl, aminocarbonyl, (di)alkylaminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, morpholinocarbonyl, alkylpiperazinylcarbonyl; C = (oxy)alkenyl, O; D = (substituted) pyrrolidinyl, piperidinyl, hexahydroazepinyl, piperazinyl, etc.], were prepared Thus, a mixture of CH2:CHCO2H and Et3N was stirred for 45 min at -50° with CH2:CHCO2Cl in THF followed by dropwise addition of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)quinazoline (preparation given) in THF for 20 min and stirring at 0° up to completely conversion to give 31% 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 12 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402496-84-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402496-84-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 47 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:122440 CAPLUS
DOCUMENT NUMBER: 137:329330

10/ 023,099

TITLE: Evaluation of the human serum albumin column as a discovery screening tool for plasma protein binding

AUTHOR(S): Buchholz, Lisa; Cai, Chun-Hua; Andress, Larry; Cleton, Adriaan; Brodfuehrer, Joanne; Cohen, Lucinda

CORPORATE SOURCE: Dynamics and Metabolism, Department of Pharmacokinetics, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA

SOURCE: European Journal of Pharmaceutical Sciences (2002), 15(2), 209-215
CODEN: EPSCED; ISSN: 0928-0987

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

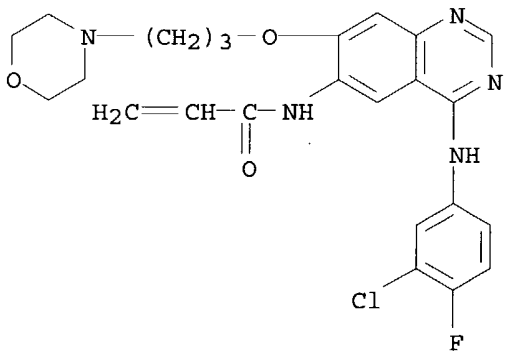
LANGUAGE: English

AB A total of 69 compds. with a variety of chemical structures were assayed using a human serum albumin column in combination with UV and mass spectrometric detection. A moderate correlation, R2=0.661, between the plasma protein binding, determined by traditional techniques of equilibrium dialysis or ultrafiltration, and chromatog. retention factor (k'/k'+1) was observed Disparity between the regression line and numerous samples was observed across the entire range of plasma protein binding. Attempts to discriminate between compds. from the data set to achieve better correlation based physico-chemical properties were unsuccessful. Good agreement was observed for retention times obtained with UV detection with mobile phase containing phosphate buffer and mass spectrometric detection with mobile phase containing acetate buffer. Essentially identical data were obtained for compds. analyzed in singlet or cassette for minimally or highly bound (>90% bound) compds. Anal. of cassettes containing compds. with plasma protein binding greater than 90% did not cause column overload, even at analyte concns. up to 100 μg/mL. Diverse results were obtained when chromatog. retention was used to rank order various classes of compds. Better correlation with ordering from known binding was obtained when a compound class contained a wide range of protein binding, in contrast to when compds. within a given class were all highly bound.

XT **289499-45-2**, PD 0183805
RL: ANT (Analyte); ANST (Analytical study)
(evaluation of human serum albumin column as a discovery screening tool for plasma protein binding)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

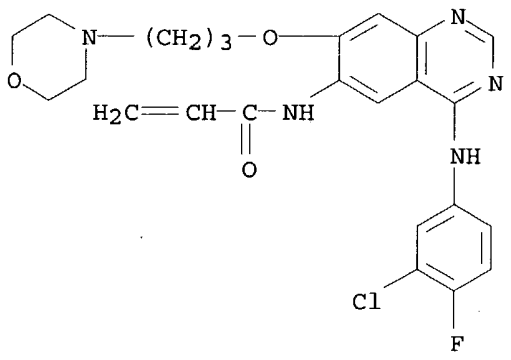
L3 ANSWER 48 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:86818 CAPLUS
DOCUMENT NUMBER: 136:395481
TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family
AUTHOR(S): Bishop, Philippe C.; Myers, Timothy; Robey, Robert; Fry, David W.; Liu, Edison T.; Blagosklonny, Mikhail V.; Bates, Susan E.
CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, MD, 20892, USA
SOURCE: Oncogene (2002), 21(1), 119-127
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. responses to the HER1 (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have observed similar results in the 60 cell lines of the NC1 Anti-Cancer Drug Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concns. of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at submicromolar concns. of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 M) but concns. that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

IT **289499-45-2**, NSC 709239
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PD 183805; sensitivity of cancer cells to inhibitors of EGF receptor family)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

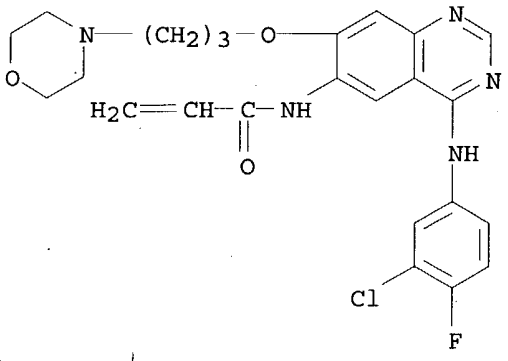
10/ 023,099



●2 HCl

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 49 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:74864 CAPLUS
DOCUMENT NUMBER: 137:134227
TITLE: Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Adjei, Alex A.
CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SOURCE: Drugs of the Future (2001), 26(11), 1087-1092
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.
IT **289499-45-2**, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy)
RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 50 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:10449 CAPLUS
DOCUMENT NUMBER: 136:74658
TITLE: Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl]acrylamide dihydrochloride
INVENTOR(S): Barth, Hubert; Steiner, Klaus; Schneider, Simon; Huels, Dietmar; Muehlenfeld, Andreas; Westermayer, Manfred
PATENT ASSIGNEE(S): Goedecke G.m.b.H., Germany
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000630	A1	20020103	WO 2001-EP6733	20010615
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10031971	A1	20020110	DE 2000-10031971	20000630
EP 1299363	A1	20030409	EP 2001-962739	20010615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001012082	A	20030506	BR 2001-12082	20010615
JP 2004501902	T2	20040122	JP 2002-505378	20010615
NZ 522001	A	20040730	NZ 2001-522001	20010615
EE 200200714	A	20040816	EE 2002-714	20010615
ZA 2002009717	A	20031201	ZA 2002-9717	20021129
BG 107352	A	20030731	BG 2002-107352	20021204
NO 2002006193	A	20030127	NO 2002-6193	20021223
US 2004034022	A1	20040219	US 2003-312173	20030404

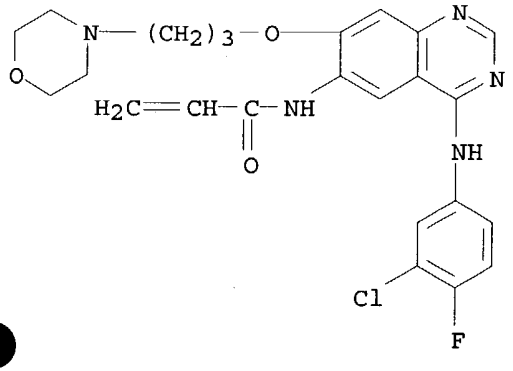
10/ 023,099

PRIORITY APPLN. INFO.: DE 2000-10031971 A 20000630
WO 2001-EP6733 W 20010615

AB Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide-2HCl (I), processes for their preparation, as well as their use for the preparation of pharmaceuticals with irreversible tyrosine kinase inhibiting action are described. N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide was dissolved in EtOH and treated with HCl to give I monohydrate (Form M). The compound was thermally stable when subjected to different thermal stress conditions.

IT **289499-45-2P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of polymorphic forms/hydrates of (chlorofluorophenylamino)morpholinylpropoxyquinazolinylacrylamide)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 51 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:935435 CAPLUS
DOCUMENT NUMBER: 136:84677
TITLE: Methods for enhancing antibody-induced cell lysis and treating cancer
INVENTOR(S): Weiner, George; Hartmann, Gunther
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 312 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097843	A2	20011227	WO 2001-US20154	20010622
WO 2001097843	A3	20030123		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

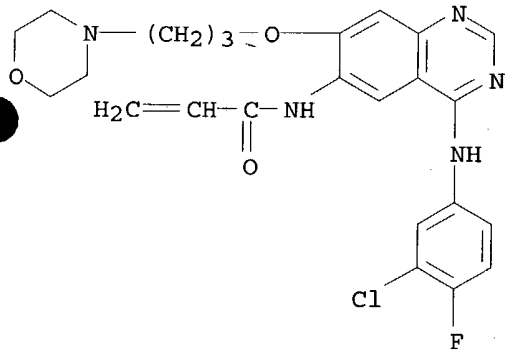
CA 2410371	AA	20011227	CA 2001-2410371	20010622
US 2003026801	A1	20030206	US 2001-888326	20010622
EP 1296714	A2	20030402	EP 2001-948684	20010622
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535907	T2	20031202	JP 2002-503327	20010622
PRIORITY APPLN. INFO.:			US 2000-213346P	P 20000622
			WO 2001-US20154	W 20010622

AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

IT **289499-45-2**, PD 183805
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 52 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2001:921399 CAPLUS
DOCUMENT NUMBER:	137:72358
TITLE:	CI-1033, a pan-erbB tyrosine kinase inhibitor
AUTHOR(S):	Slichenmyer, William J.; Elliott, William L.; Fry, David W.
CORPORATE SOURCE:	Department of Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE:	Seminars in Oncology (2001), 28(5, Suppl. 16), 80-85 CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER:	W. B. Saunders Co.
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

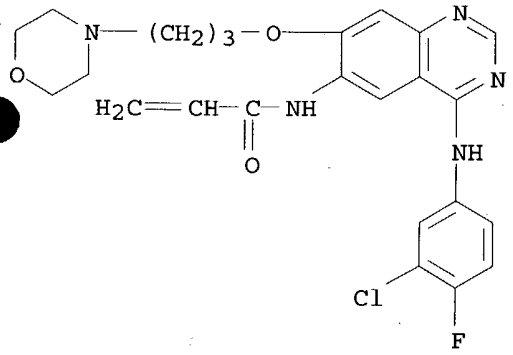
AB A review. Overexpression of the erbB family of receptor tyrosine kinases

has been implicated in a variety of tumors including breast, lung, prostate, and brain. Most solid tumors express one or more of these receptors, which can often be related to tumor aggressiveness and poor patient prognosis. CI-1033, a pan-erbB tyrosine kinase inhibitor, is a clin. promising agent that is active against all four members of the erbB receptor tyrosine kinase family. In vitro studies of human cancer cell lines indicate that CI-1033 results in prompt, potent, and sustained inhibition of tyrosine kinase activity. This inhibition is highly selective for erbBI (epidermal growth factor receptor), erbB2, erbB3, and erbB4 without inhibiting tyrosine kinase activity of receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin receptor, even at high concns. Treatment of athymic nude mice bearing xenografts of human A431 epidermoid carcinoma, H125 non-small cell lung carcinoma, and SF-767 glioblastoma results in highly significant suppression of tumor growth. The major toxicity in animals is diarrhea, which is more severe at higher doses. In animal models, all side effects are reversible on cessation of treatment. Thus, CI-1033, which is currently undergoing phase I clin. trials, holds significant potential for use in a broad range of solid tumors.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1033, a pan-erbB tyrosine kinase inhibitor)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 53 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:921398 CAPLUS
DOCUMENT NUMBER: 137:87979
TITLE: Anticancer therapy targeting the ErbB family of receptor tyrosine kinases
AUTHOR(S): Slichenmyer, William J.; Fry, David W.
CORPORATE SOURCE: Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 67-79
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.

10/ 023,099

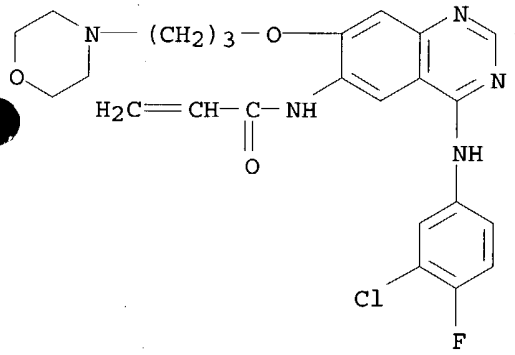
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast cancer when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer therapy targeting the ErbB family of receptor tyrosine kinases)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 54 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:800795 CAPLUS
DOCUMENT NUMBER: 136:95729
TITLE: Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of cisplatin and the new irreversible tyrosine kinase inhibitor CI-1033
AUTHOR(S): Gieseg, Michael A.; De Bock, Charles; Ferguson, Lynnette R.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, 1000, N. Z.

10/ 023,099

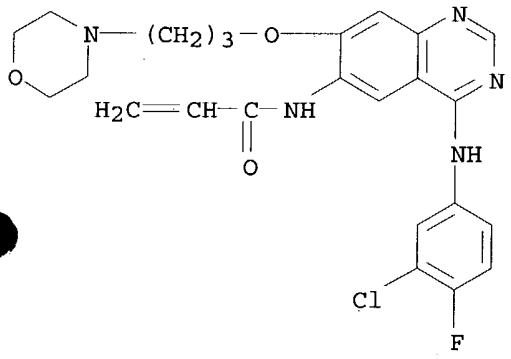
SOURCE: Anti-Cancer Drugs (2001), 12(8), 683-690
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irreversible inhibitors of the epidermal growth factor receptor (EGFR) are showing promise in clin. trials. This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with cisplatin, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy between the irreversible EGFR inhibitor and cisplatin does not appear to involve the repair of DNA-cisplatin adducts. Given the current clin. data, this combination may be of more than theor. interest.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evidence for EGFR-enhanced chemosensitivity in combinations of cisplatin and CI-1033)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 55 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:799778 CAPLUS
DOCUMENT NUMBER: 136:112324
TITLE: Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation
AUTHOR(S): Dowlati, Afshin; Haaga, John; Remick, Scot C.; Spiro, Timothy P.; Gerson, Stanton L.; Liu, Lili; Berger, Sosamma J.; Berger, Nathan A.; Willson, James K. V.
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine and Developmental Therapeutics Program, Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA
SOURCE: Clinical Cancer Research (2001), 7(10), 2971-2976
CODEN: CCREF4; ISSN: 1078-0432

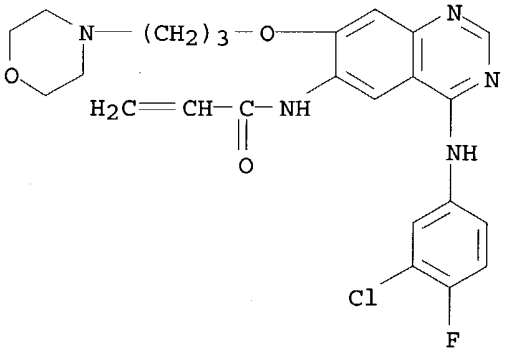
10/ 023,099

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the setting of target-based anticancer drug development, it is critical to establish that the observed preclin. activity can be attributed to modulation of the intended target in early phase trials in human subjects. This paradigm of target modulation allows the authors to determine a Phase II or III dose (optimal biochem./biol. modulatory dose) that may not necessarily be the maximum tolerated dose. A major obstacle to target-based (often cytostatic) drug development has been obtaining relevant tumor tissue during clin. trials of these novel agents for laboratory anal. of the putative marker of drug effect. From 1989 to present, the authors have completed seven clin. trials in which the end point was a biochem. or biol. modulatory dose in human tumor tissues (not surrogate tissue). Eligibility enrollment required that patients have a biopsiable lesion either with computerized tomog. (CT) guidance or direct visualization and consent to sequential (pre and posttreatment) biopsies. A total of 192 biopsies were performed in 107 patients. All but 8 patients had sequential pre and posttreatment biopsies. Seventy-eight (73%) of the 107 patients had liver lesion biopsies. In eight patients, either one or both biopsies contained insufficient viable tumor tissue or no tumor tissue at all for anal. Of a total of 99 patients in whom the authors attempted to obtain paired biopsies, a total of 87 (88%) were successful. Reasons for failure included patient refusal for a second biopsy (n = 2), vasovagal reaction with first biopsy precluding a second biopsy (n = 1), subcapsular hepatic bleeding (n = 1), and most commonly obtaining necrotic tumor, fibrous, or normal tissue in one of the two sequential biopsies (n = 8). This is the first and largest reported series demonstrating that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early phase clin. trials.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

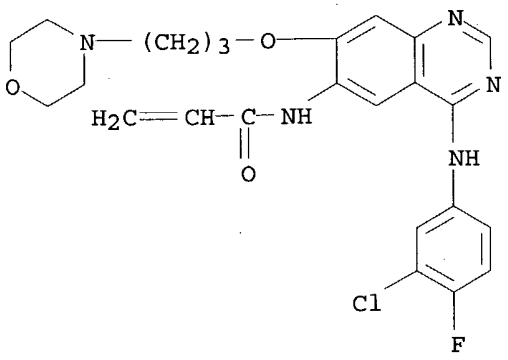
L3 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:799777 CAPLUS
DOCUMENT NUMBER: 137:27578
TITLE: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor
AUTHOR(S): Ciardiello, Fortunato; Tortora, Giampaolo
CORPORATE SOURCE: Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(10), 2958-2970
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

IT **289499-45-2**, PD183805
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting the epidermal growth factor receptor as a novel approach in the treatment of cancer)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 57 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:762992 CAPLUS
DOCUMENT NUMBER: 135:303907
TITLE: Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

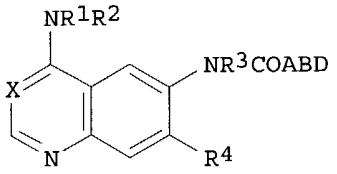
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10017539	A1	20011011	DE 2000-10017539	20000408
DE 10040525	A1	20020228	DE 2000-10040525	20000818
CA 2403152	AA	20011018	CA 2001-2403152	20010331
AU 2001063831	A5	20011023	AU 2001-63831	20010331
EP 1280798	A1	20030205	EP 2001-938076	20010331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003530395	T2	20031014	JP 2001-575577	20010331

PRIORITY APPLN. INFO.:
DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
WO 2001-EP3694 W 20010331

OTHER SOURCE(S): MARPAT 135:303907

10/ 023,099

GI



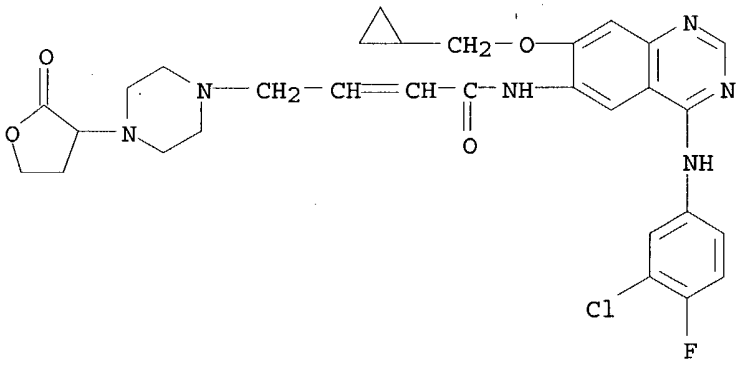
I

AB Title compds. [I; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH2CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond, (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.], were prepared Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline (preparation given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temperature to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.05 nM.

IT **365532-35-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

RN 365532-35-0 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 58 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:747043 CAPLUS

DOCUMENT NUMBER: 135:303901

TITLE: Bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction

INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany

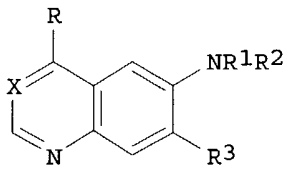
10/ 023,099

SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

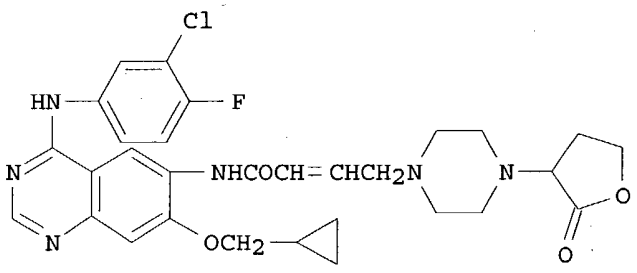
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10017539	A1	20011011	DE 2000-10017539	20000408
US 2001044435	A1	20011122	US 2001-816003	20010323
US 6627634	B2	20030930		
CA 2403152	AA	20011018	CA 2001-2403152	20010331
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001063831	A5	20011023	AU 2001-63831	20010331
EP 1280798	A1	20030205	EP 2001-938076	20010331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003530395	T2	20031014	JP 2001-575577	20010331

PRIORITY APPLN. INFO.:
DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
WO 2001-EP3694 W 20010331

OTHER SOURCE(S): MARPAT 135:303901
GI



I



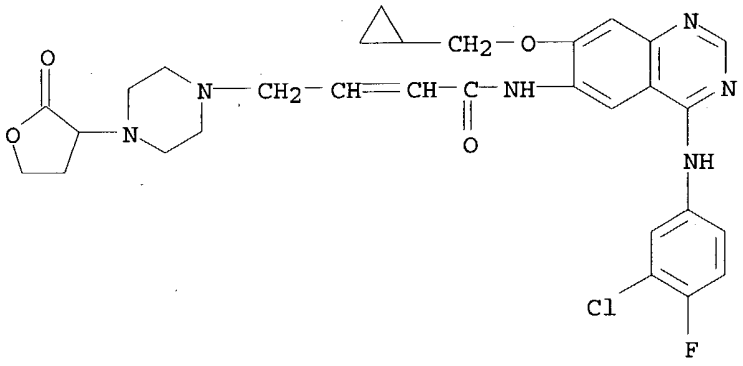
II

AB Bicyclic heterocycles I [X = N, CCN; R = substituted NH2; R1 = H, alkyl; R2 = acyl; R3 = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy] were prepared for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by reduction

to the amine, reaction with 4-bromocrotonic acid and N-tert.-butoxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC50 for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

IT **365532-35-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

RN 365532-35-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 59 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:713163 CAPLUS
DOCUMENT NUMBER: 135:267215
TITLE: Combined treatment with keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor for reducing EGFR inhibitor-associated epithelial toxicity
INVENTOR(S): Miller, Penelope Elizabeth; Moyer, James Dale
PATENT ASSIGNEE(S): Pfizer Products, Inc., USA; OSI Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070255	A2	20010927	WO 2001-US8207	20010315
WO 2001070255	A3	20020228		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2403721	AA	20010927	CA 2001-2403721	20010315
US 2002061304	A1	20020523	US 2001-808751	20010315
EP 1276496	A2	20030122	EP 2001-916662	20010315

10/ 023,099

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

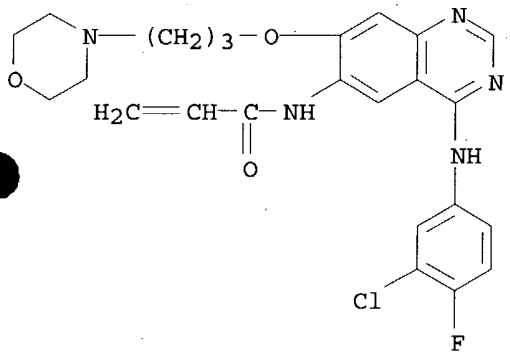
JP 2003527437	T2	20030916	JP 2001-568452		20010315
US 2004071697	A1	20040415	US 2003-458072		20030610
PRIORITY APPLN. INFO.:			US 2000-190697P	P	20000320
			US 2001-808751	B1	20010315
			WO 2001-US8207	W	20010315

AB Compns. and methods are provided for treating the epithelial toxicity caused by administering to a human cancer patient an epidermal growth factor receptor (EGFR) inhibitor. The pharmaceutical composition preferably comprises an EGFR inhibitor and a keratinocyte growth factor (KGF) in a pharmaceutically acceptable carrier. The method of treatment comprises co-administering to the patient a therapeutically effective amount of KGF with the EGFR inhibitor.

IT **289499-45-2**, PD 183805
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor combination treatment for reducing EGFR inhibitor-associated epithelial toxicity)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L3 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

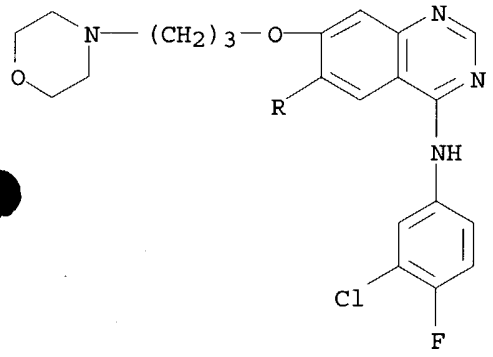
ACCESSION NUMBER:	2001:516932 CAPLUS
DOCUMENT NUMBER:	135:313144
TITLE:	The 4-anilinoquinazoline class of inhibitors of the erbB family of receptor tyrosine kinases
AUTHOR(S):	Denny, William A.
CORPORATE SOURCE:	Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE:	Farmaco (2001), 56(1-2), 51-56 CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER:	Elsevier Science S.A.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

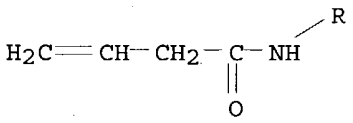
AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer

drugs. The substrate protein binding site theor. is the more attractive intracellular target on these enzymes, possessing lower homol. than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationships shown by these compds. suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-773) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-anilinoquinazoline analogs (two reversible and one irreversible inhibitor) have been evaluated clin. as anticancer drugs. Data from the most advanced, the reversible inhibitor Iressa, suggest that this class of compds. may be of value in cancer chemotherapy.

IT **367518-74-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(4-anilinoquinazoline class of inhibitors of erbB family of receptor tyrosine kinases)

RN 367518-74-9 CAPLUS
CN 3-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)





REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 61 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:380438 CAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA
SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

10/ 023,099

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2391534	AA	20010525	CA 2000-2391534	20001114
AU 2001016075	A5	20010530	AU 2001-16075	20001114
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003138432	A1	20030724	US 2000-738625	20001215
PRIORITY APPLN. INFO.:			US 1999-165485P	P 19991115
			US 2000-239478P	P 20001011
			US 2000-241937P	P 20001020
			US 2000-241939P	P 20001020
			WO 2000-US31262	W 20001114
			US 2000-712465	B1 20001115

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

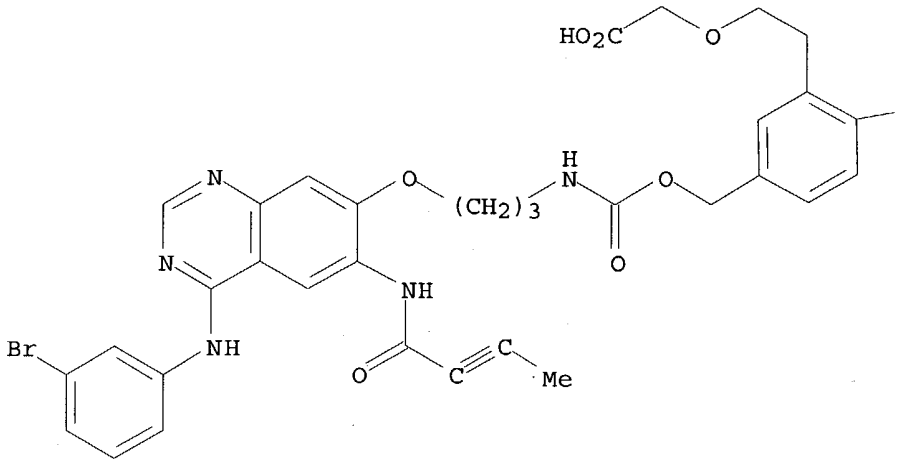
IT **341551-76-6P**
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341551-76-6 CAPLUS

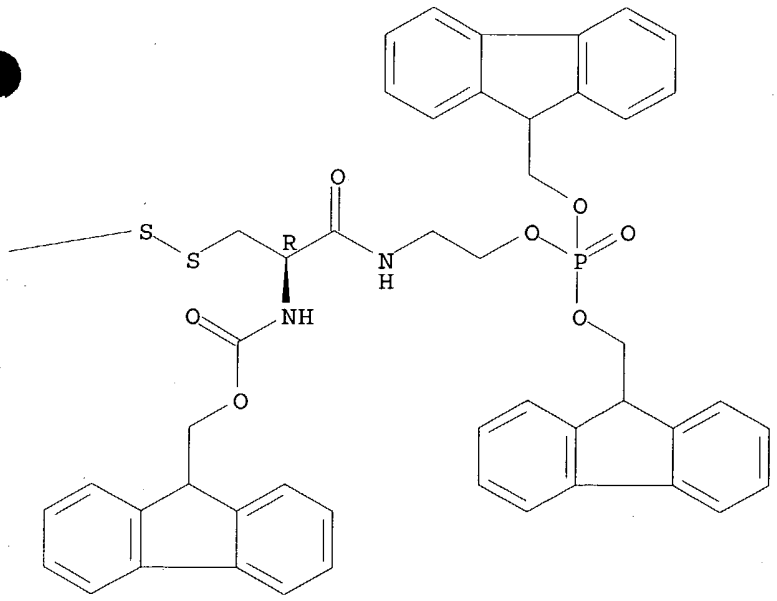
CN 2,4-Dioxa-7,10-diaza-3-phosphaundecan-11-oic acid, 9-[[[4-[[[[[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-butynyl)amino]-7-quinazolinyl]oxy]propyl]amino]carbonyl]oxy]methyl]-2-[2-(carboxymethoxy)ethyl]phenyl]dithio]methyl]-1-(9H-fluoren-9-yl)-3-(9H-fluoren-9-ylmethoxy)-8-oxo-, 11-(9H-fluoren-9-ylmethyl) ester, 3-oxide, (9R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L3 ANSWER 62 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:367797 CAPLUS
DOCUMENT NUMBER: 135:102151
TITLE: Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition
AUTHOR(S): Nelson, James M.; Fry, David W.
CORPORATE SOURCE: Pfizer Global Research and Development, Ann Arbor, MI,

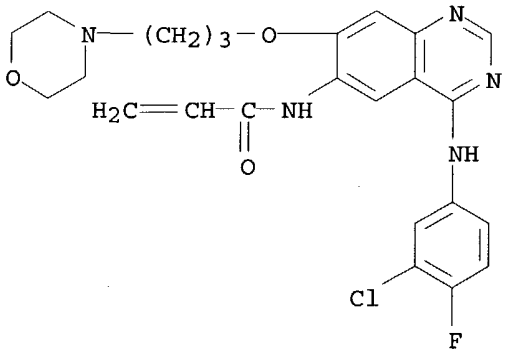
48105, USA
SOURCE: Journal of Biological Chemistry (2001), 276(18), 14842-14847
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is over-expressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the ErbB-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. P38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in human breast carcinoma in response to ErbB receptor family inhibition)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 63 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:338332 CAPLUS
DOCUMENT NUMBER: 134:336209
TITLE: EGFR tyrosine kinase inhibitors for the prevention of breast cancer
INVENTOR(S): Bundred, Nigel James
PATENT ASSIGNEE(S): The University of Manchester, UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032155	A2	20010510	WO 2000-GB4190	20001101
WO 2001032155	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2389411	AA	20010510	CA 2000-2389411	20001101
BR 2000015194	A	20020618	BR 2000-15194	20001101
EP 1272188	A2	20030108	EP 2000-973002	20001101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003513035	T2	20030408	JP 2001-534360	20001101
NO 2002002065	A	20020624	NO 2002-2065	20020430
ZA 2002003431	A	20021209	ZA 2002-3431	20020430

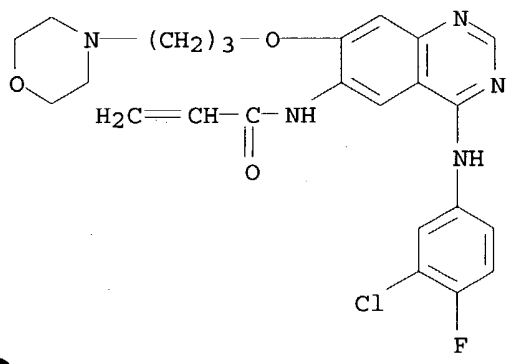
PRIORITY APPLN. INFO.: GB 1999-25958 A 19991102
WO 2000-GB4190 W 20001101

AB An EGFR tyrosine kinase inhibitor (e.g. ZD1839) is used in the manufacture of a medicament for use in (a) reducing the transformation of epithelial cells from a normal to a malignant state in an invasive breast cancer free human; and/or (b) reducing the transformation of epithelial cells from an intermediate state, between normal epithelium and malignant invasive epithelium, to a malignant state in an invasive breast cancer free human; and/or (c) causing substantial reversion of epithelial tissue back to a normal state from an intermediate state between normal epithelium and malignant invasive epithelium.

IT **289499-45-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGFR tyrosine kinase inhibitors for the prevention of breast cancer)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

10/ 023,099



●2 HCl

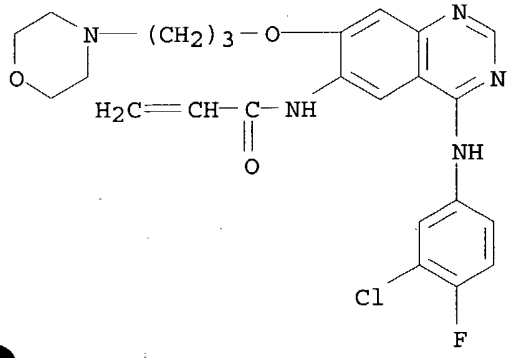
L3 ANSWER 64 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:125550 CAPLUS
DOCUMENT NUMBER: 134:348032
TITLE: The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and topotecan by inhibiting breast cancer resistance protein-mediated drug efflux
AUTHOR(S): Erlichman, Charles; Boerner, Scott A.; Hallgren, Christopher G.; Spieker, Rebecca; Wang, Xiao-Yang; James, C. David; Scheffer, George L.; Maliepaard, Marc; Ross, Douglas D.; Bible, Keith C.; Kaufmann, Scott H.
CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic, Mayo Graduate School, Rochester, MN, 55905, USA
SOURCE: Cancer Research (2001), 61(2), 739-748
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because the activities of HER family members are elevated and/or aberrant in a variety of human neoplasms, these cell surface receptors are receiving increasing attention as potential therapeutic targets. In the present study, we examined the effect of combining the HER family tyrosine kinase inhibitor CI1033 (PD 183805) with the topoisomerase (topo) I poison 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, in a number of different cell lines. Colony-forming assays revealed that the antiproliferative effects of simultaneous treatment with CI1033 and SN-38 were synergistic in T98G glioblastoma cells and HCT8 colorectal carcinoma cells, whereas sequential treatments were additive at best. In addnl. studies examining the mechanistic basis for these findings in T98G cells, immunoblotting revealed that the inhibitory effects of CI1033 on epidermal growth factor receptor autophosphorylation were unaffected by SN-38. Likewise, CI1033 had no effect on topo I polypeptide levels, localization, or activity. Nonetheless, CI1033 markedly enhanced the number of covalent topo I-DNA complexes stabilized by SN-38 or the related agent topotecan (TPT). Anal. of intracellular SN-38 levels by high-performance liquid chromatog. and intracellular TPT levels by flow microfluorometry revealed that CI1033 increased the steady-state accumulation of SN-38 and TPT by 9.4 ± 1.9- and 1.8 ± 0.2-fold, resp. Further evaluation revealed that the initial rate of TPT uptake was unaffected by CI1033, whereas the rate of efflux was markedly diminished. Addnl. studies demonstrated that T98G and HCT8 cells express the breast

cancer resistance protein (BCRP), a recently cloned ATP binding cassette transporter. Moreover, CI1033 enhanced the uptake and cytotoxicity of SN-38 and TPT in cells transfected with BCRP but not empty vector. Conversely, CI1033 accumulation was diminished in cells expressing BCRP, suggesting that CI1033 is a substrate for this efflux pump. These results indicate that CI1033 can modulate the accumulation and subsequent cytotoxicity of two widely used topo I poisons in cells that have no history of previous exposure to these agents.

IT **289499-45-2**, CI 1033
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(HER tyrosine kinase inhibitor CI1033 interactions with SN-38 and topotecan in cancer treatment)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 65 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:911231 CAPLUS
DOCUMENT NUMBER: 134:71599
TITLE: Preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Metz, Thomas; Solca, Flavio; Jung, Birgit; Baum, Anke
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

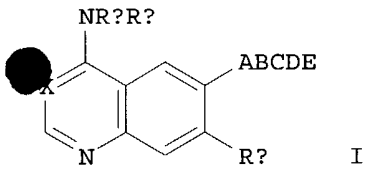
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078735	A1	20001228	WO 2000-EP5547	20000616
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,				

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

DE 19928281	A1	20001228	DE 1999-19928281	19990621
DE 10023085	A1	20011115	DE 2000-10023085	20000511
CA 2375259	AA	20001228	CA 2000-2375259	20000616
BR 2000011834	A	20020312	BR 2000-11834	20000616
EP 1194418	A1	20020410	EP 2000-936888	20000616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200103692	T2	20021021	TR 2001-200103692	20000616
JP 2003502410	T2	20030121	JP 2001-504901	20000616
EE 200100695	A	20030217	EE 2001-695	20000616
AU 775285	B2	20040729	AU 2000-52214	20000616
NZ 516633	A	20040924	NZ 2000-516633	20000616
BG 106189	A	20020830	BG 2001-106189	20011207
US 2002169180	A1	20021114	US 2001-16280	20011210
NO 2001006185	A	20011218	NO 2001-6185	20011218
ZA 2001010351	A	20020618	ZA 2001-10351	20011218

PRIORITY APPLN. INFO.:	DE 1999-19928281	A	19990621
	US 1999-146644P	P	19990730
	DE 2000-10023085	A	20000511
	WO 2000-EP5547	W	20000616

OTHER SOURCE(S): MARPAT 134:71599
GI



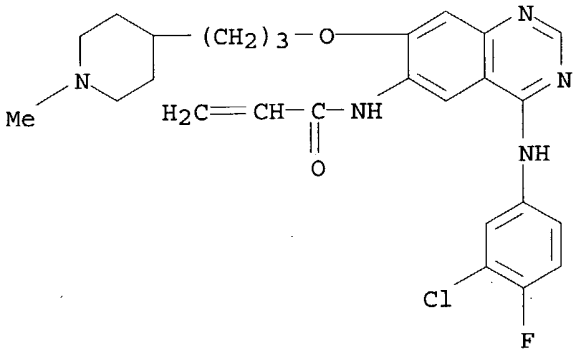
I

AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, PhCH2CH2; Rc = (substituted) cycloalkoxy, cycloalkylalkoxy; A = (alkyl-substituted) imino; B = CO, SO2; C = (substituted) allenylene, vinylene, butadienylene, ethynylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, carbonyloxyalkylene, carbonyliminoalkylene, bond, etc.; E = amino, (substituted) alkylamino, dialkylamino, etc.], were prepared Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxy]quinazoline (preparation given) in CH2Cl2 containing Et3N at -10° was treated with acryloyl chloride in THF to give 35% 4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation of F/L HERC cells with IC50 = <0.35 nM.

IT **314771-08-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors)

RN 314771-08-9 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



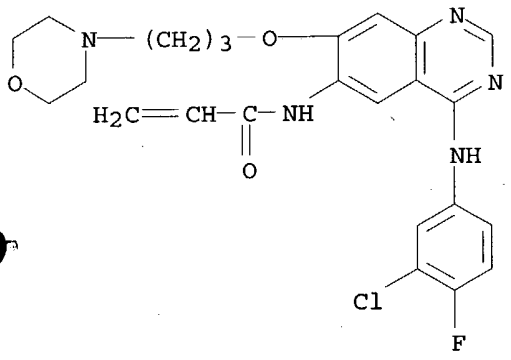
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 66 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:828300 CAPLUS
DOCUMENT NUMBER: 135:57892
TITLE: Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor
AUTHOR(S): Rao, G. S.; Murray, S.; Ethier, S. P.
CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA
SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 48(5), 1519-1528
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: Overexpression of the ErbB family of growth factor receptors is present in a wide variety of human tumors and is correlated with poor prognosis. The purpose of this study was to determine the effects of a novel small mol. ErbB tyrosine kinase inhibitor, CI-1033, in combination with ionizing radiation on breast cancer cell growth and survival. Materials & Methods: Growth assays were performed on ErbB-overexpressing human breast cancer cells developed in our laboratory in the presence of 0.1-1.0 μM CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing radiation with or without CI-1033. For some expts., clonogen nos., defined as the product of surviving fraction and total number of cells, were calculated at each time point during a course of multifraction radiation. Results: CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. A single 48-h exposure of 1 μM CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and radiation (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to radiation alone. In a multifraction experiment, exposure to CI-1033 and three 5-Gy fractions of gamma radiation decreased the total number of clonogens in the population by 65-fold compared to radiation alone. Conclusion: CI-1033 results in potent growth inhibition and modest cytotoxicity of ErbB-overexpressing breast cancer cells, and has synergistic effects when combined with ionizing radiation. These data suggest that CI-1033 may have excellent clin. potential both alone and in combination with radiation therapy.

IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization of human breast cancer cells by ErbB family

receptor tyrosine kinase inhibitor)
RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

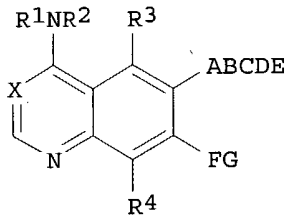
L3 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:628125 CAPLUS
DOCUMENT NUMBER: 133:207919
TITLE: Preparation of 4-amino-quinazoline and quinoline derivatives having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas; Solca, Flavio; Blech, Stefan
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 232 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19908567	A1	20000831	DE 1999-19908567	19990227
DE 19911366	A1	20000921	DE 1999-19911366	19990315
DE 19928306	A1	20001228	DE 1999-19928306	19990621
DE 19954816	A1	20010517	DE 1999-19954816	19991113
CA 2361174	AA	20000908	CA 2000-2361174	20000224
EP 1157011	A1	20011128	EP 2000-910695	20000224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008524	A	20011218	BR 2000-8524	20000224

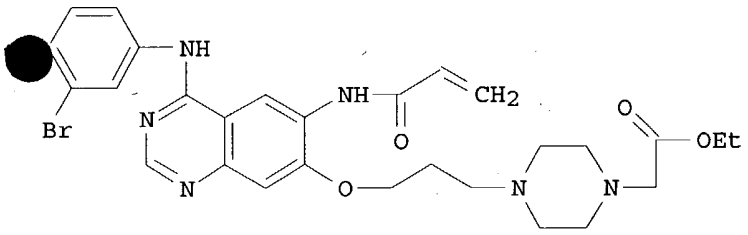
JP 2002538145	T2	20021112	JP 2000-602218		20000224
EE 200100449	A	20021216	EE 2001-449		20000224
BG 105765	A	20020329	BG 2001-105765		20010801
HR 2001000617	A1	20021031	HR 2001-617		20010823
NO 2001004114	A	20011015	NO 2001-4114		20010824
PRIORITY APPLN. INFO.:			DE 1999-19908567	A	19990227
			DE 1999-19911366	A	19990315
			DE 1999-19928306	A	19990621
			US 1999-149329P	P	19990817
			DE 1999-19954816	A	19991113
			WO 2000-EP1496	W	20000224

OTHER SOURCE(S): MARPAT 133:207919

GI



I



II

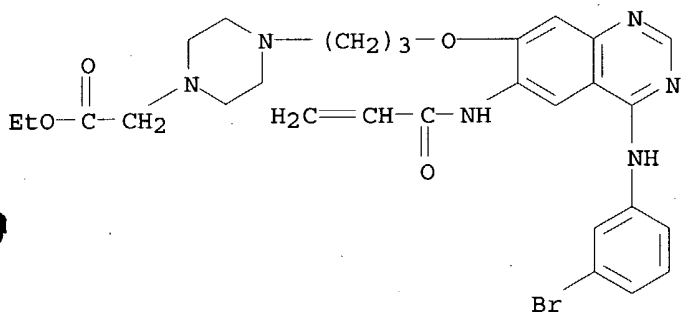
AB Title compds. [I; R1 = H, C1-C4-alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3, R4 independently = H, F, Cl, CH3O, CH3OCH2, (CH3)2NCH2, (CH3CH2)2NCH2, pyrrolidino, piperidino, morpholino; X = C(CN), N; A = O, NH, (C1-C4)-alkylN; B = CO, SO2; C = 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, 1,3-butadien-1,4-ylene, with CH3, CF3 substitution; D = alkylene, CO-alkylene, SO2-alkylene; CO, SO2; E = HOCO(CH2)nNR5, (HO)2P(:O)(CH2)nNR5; n = 1-6; R5 = H, alkyl], tautomers, stereoisomers, and physiol. acceptable salts are prepared and having valuable pharmacol. properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases. Title compds. are useful for treating tumoral diseases, diseases of the lungs and respiratory tract. Thus, the title compound II was prepared and tested by Cell Titer 96TM Aqueous Nonradioactive Cell Proliferation Assay.

IT **289700-58-9P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract

diseases)
RN 289700-58-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 68 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:607393 CAPLUS
DOCUMENT NUMBER: 133:207916
TITLE: Preparation of aminoquinazolines as epidermal growth factor receptor inhibitors.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K-G, Germany
SOURCE: Ger. Offen., 26 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908567	A1	20000831	DE 1999-19908567	19990227
CA 2361174	AA	20000908	CA 2000-2361174	20000224
WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 513802	A	20010928	NZ 2000-513802	20000224
EP 1157011	A1	20011128	EP 2000-910695	20000224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008524	A	20011218	BR 2000-8524	20000224
JP 2002538145	T2	20021112	JP 2000-602218	20000224
EE 200100449	A	20021216	EE 2001-449	20000224
ZA 2001005983	A	20020920	ZA 2001-5983	20010720
BG 105765	A	20020329	BG 2001-105765	20010801
HR 2001000617	A1	20021031	HR 2001-617	20010823
NO 2001004114	A	20011015	NO 2001-4114	20010824

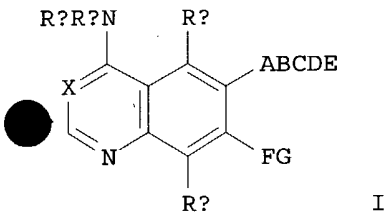
10/ 023,099

PRIORITY APPLN. INFO.:

DE 1999-19908567	A	19990227
DE 1999-19911366	A	19990315
DE 1999-19928306	A	19990621
US 1999-149329P	P	19990817
DE 1999-19954816	A	19991113
WO 2000-EP1496	W	20000224

OTHER SOURCE(S): MARPAT 133:207916

GI



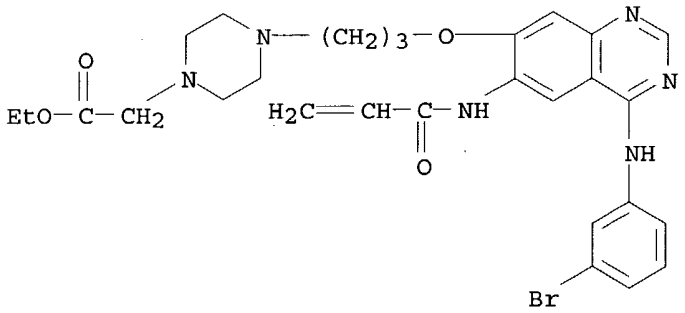
I

AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, 1-phenylethyl; Rc, Rm = H, F, Cl, MeO, (methoxy-, dimethylamino-, diethylamino-, pyrrolidino-, piperidino-, morpholino- substituted) Me; X = N, NCC; A = O, alkylimino; B = CO, SO2; C = (Me- or F3C-substituted) allenylene, vinylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, etc.; E, G = (substituted) R602CYNR5, etc.; R5 = H, (substituted) alkyl; R6 = H, (substituted) alkyl, cycloalkyl, alkenyl, alkynyl, etc.; F = alkylene, oxyalkylene, O; FG = H, F, Cl, alkoxy, etc.], were prepared Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methylpiperazin-1-yl]propoxy]quinazoline (preparation given) in CH2Cl2 containing Et3N was treated with acryloyl chloride in CH2Cl2 at -10° to give 62% 4-[(3-bromophenyl)amino]-7-[3-[4-[(ethoxycarbonyl)methyl]piperazin-1-yl]propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation with IC50 = 2.6 nM.

IT **289700-58-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoquinazolines as epidermal growth factor receptor inhibitors)

RN 289700-58-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



L3 ANSWER 69 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

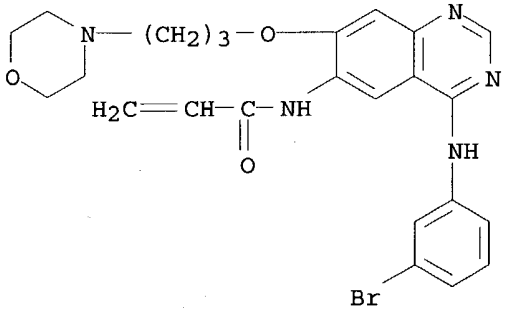
10/ 023,099

ACCESSION NUMBER: 2000:481416 CAPLUS
DOCUMENT NUMBER: 134:216784
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty Medical and Health Sciences, The Univ. Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 3199
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Six author names were inadvertently omitted from the author contribution line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Rewcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter, David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.

IT **198959-99-8P**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))

RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 70 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:368316 CAPLUS
DOCUMENT NUMBER: 133:4672
TITLE: Preparation of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases
INVENTOR(S): Bridges, Alexander James; Driscoll, Denise; Klohs, Wayne Daniel
PATENT ASSIGNEE(S): Warner-Lambert Co., USA
SOURCE: PCT Int. Appl., 33 pp.

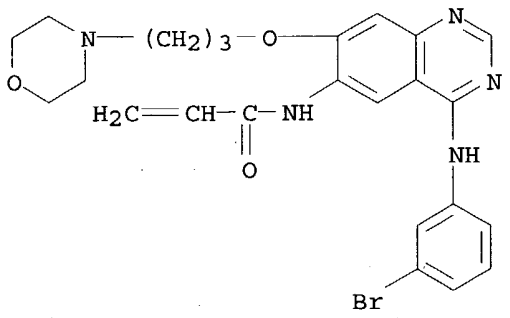
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031048	A1	20000602	WO 1999-US22116	19990923
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2349721	AA	20000602	CA 1999-2349721	19990923
AU 9962612	A1	20000613	AU 1999-62612	19990923
AU 763626	B2	20030731		
BR 9915487	A	20010731	BR 1999-15487	19990923
EP 1131304	A1	20010912	EP 1999-949821	19990923
EP 1131304	B1	20021204		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002530386	T2	20020917	JP 2000-583876	19990923
EE 200100271	A	20021015	EE 2001-271	19990923
AT 229008	E	20021215	AT 1999-949821	19990923
ES 2188254	T3	20030616	ES 1999-949821	19990923
NZ 512189	A	20031031	NZ 1999-512189	19990923
SK 283688	B6	20031202	SK 2001-657	19990923
ZA 2001003535	A	20020802	ZA 2001-3535	20010502
US 6344455	B1	20020205	US 2001-831991	20010516
NO 2001002465	A	20010713	NO 2001-2465	20010518
BG 105608	A	20020131	BG 2001-105608	20010615
PRIORITY APPLN. INFO.:			US 1998-109065P P	19981119
			WO 1999-US22116 W	19990923

AB The title compound that is an irreversible inhibitor of tyrosine kinases such as EGFR, erbB2, and erbB4, and inhibitor of the tyrosine phosphorylation of erbB3 and VEGF secretion (biol. data were given), was prepared The title compound is useful in treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis.

IT **198959-99-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases)

RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

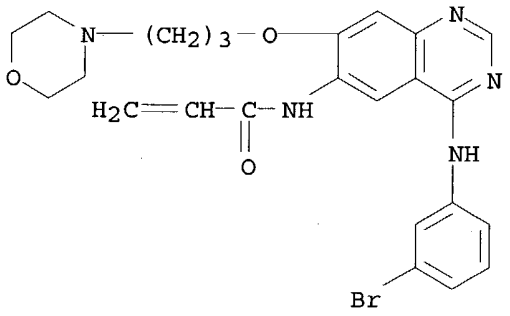
L3 ANSWER 71 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:164843 CAPLUS
DOCUMENT NUMBER: 132:317628
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference

may contribute to the observed lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

IT **198959-99-8P**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines)

RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 72 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:113656 CAPLUS
DOCUMENT NUMBER: 130:168387
TITLE: Irreversible inhibitors of tyrosine kinases
INVENTOR(S): Bridges, Alexander James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906378	A1	19990211	WO 1998-US15784	19980729
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887607	A1	19990222	AU 1998-87607	19980729
US 6127374	A	20001003	US 1999-269545	19990325
US 6562818	B1	20030513	US 2000-593031	20000613
PRIORITY APPLN. INFO.:			US 1997-54060P P	19970729
			WO 1998-US15784 W	19980729
			US 1999-269545 A3	19990325

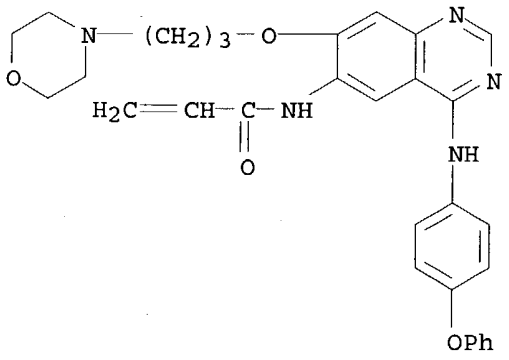
OTHER SOURCE(S): MARPAT 130:168387

AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH2OH was treated with 4-FC6H4NO2 to give 4-PhCH2OC6H4NO2, which was reduced to the amine and used to aminate 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-(4-benzyloxyanilino)quinazoline hydrochloride was reduced to the amine and acylated to give N-[4-(4-benzyloxyanilino)quinazolin-6-yl]acrylamide (I). I had an IC50 for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.

IT **220488-46-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anilinoquinazolinylacrylamides and related compds. as tyrosine kinase inhibitors)

RN 220488-46-0 CAPLUS

CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[(4-phenoxyphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 73 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:696745 CAPLUS

DOCUMENT NUMBER: 128:3695

TITLE: Preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors

INVENTOR(S): Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong; et al.

PATENT ASSIGNEE(S): Warner-Lambert Company, USA; Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong

SOURCE: PCT Int. Appl., 193 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738983	A1	19971023	WO 1997-US5778	19970408

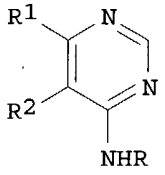
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP,

KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI,
SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG

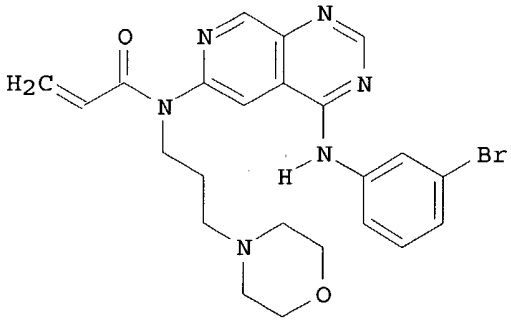
CA 2249446	AA	19971023	CA 1997-2249446		19970408
AU 9724463	A1	19971107	AU 1997-24463		19970408
AU 725533	B2	20001012			
EP 892789	A1	19990127	EP 1997-920213		19970408
EP 892789	B1	20020227			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI					
CN 1218456	A	19990602	CN 1997-194458		19970408
CN 1145614	B	20040414			
BR 9708640	A	19990803	BR 1997-8640		19970408
JP 2000508657	T2	20000711	JP 1997-537173		19970408
JP 3370340	B2	20030127			
AT 213730	E	20020315	AT 1997-920213		19970408
ES 2174250	T3	20021101	ES 1997-920213		19970408
SK 284073	B6	20040908	SK 1998-1417		19970408
ZA 9703060	A	19971104	ZA 1997-3060		19970410
BG 63160	B1	20010531	BG 1998-102811		19981001
NO 9804718	A	19981209	NO 1998-4718		19981009
KR 2000005364	A	20000125	KR 1998-708086		19981010
US 6344459	B1	20020205	US 1999-155501		19990608
US 6602863	B1	20030805	US 2000-671559		20000927
US 2003229051	A1	20031211	US 2003-441450		20030520
PRIORITY APPLN. INFO.:			US 1996-15351P	P	19960412
			WO 1997-US5778	W	19970408
			US 1999-155501	A3	19990608
			US 2000-671559	A3	20000927

OTHER SOURCE(S): MARPAT 128:3695

GI



I



II

AB Title compds. [I; R = (CHR6)pR9; R1R2 = CH:CR7CR8:CH, CH:CR7CR8:N, CH:CR7N:CH, etc.; R6 = H or alkyl; 1 of R7,R8 = Z1Z2R10 and the other = OR4, SR4, NHR3; R3,R4 = (un)substituted alkyl, heterocyclylalkyl, etc.; R9 = (un)substituted Ph; R10 = CR11:CHR5, C.tplbond.CR5, CR11:C:CHR5; R5 = H, halo, alkyl, Ph, etc.; R11 = H, halo, alkyl; Z1 = bond, O, (alkyl)imino, CH2, etc.; Z2 = CO, SO, P(O)(OH), etc.; p = 0 or 1] were prepared Thus, I (R = C6H4Br-3, R1R2 = CH:NCR8:CH, R8 = F) was condensed with 3-morpholinoprpanamine and the product acylated by CH2:CHCOCl to give title compound II. Data for biol. activity of I were given.

IT **198959-99-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)